Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Al-Hendy A, Lukes AS, Poindexter AN III, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med 2020;383:630-42. DOI: 10.1056/NEJMoa2008283

Treatment of Uterine Fibroid Symptoms With Relugolix Combination Therapy – LIBERTY 1 and LIBERTY 2 Protocols and Statistical Analysis Plan

This supplement contains the following items:

1. LIBERTY 1 Protocol
   - Amendment 2: Summary of Changes
   - Amendment 2
   - Amendment 1: Summary of Changes
   - Amendment 1
   - Original Protocol

2. LIBERTY 2 Protocol
   - Amendment 2: Summary of Changes
   - Amendment 2
   - Amendment 1: Summary of Changes
   - Amendment 1
   - Original Protocol

3. LIBERTY 1 and LIBERTY 2 Statistical Analysis Plan
   - Amendment 1: Summary of Changes
   - Amendment 1
   - Original Statistical Analysis Plan

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 08-FEB-2017 Amendment 2: 18-SEP-2017

SPONSOR SIGNATURE PAGE

LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3001

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

18- Sep- 2017
Date

18- Sep 2017
Date

18 Sept 2017
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18 Sep 2017
Date

AMENDMENT 2: SUMMARY OF CHANGES

Protocol MVT-601-3001 entitled "LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids" has been amended as described in the table below. The main purpose of the amendment was to provide clarification regarding roll-over of patients into the extension study MVT-601-3003 and follow-up assessments for patients who do not enroll in the extension study. Modifications were also made to the secondary efficacy endpoints related to disease related symptoms and impact of disease on activities, function and quality of life. This includes the addition of a new patient global assessments for function and symptoms. The amendment also includes modifications or clarifications to study eligibility as well as study procedures or tests. A detailed list of changes is described below. Note that corrections of typos, minor clarifications and minor wording changes to improve readability and understanding are not included in this table.

Item; Section(s)	Protocol Amendment 1	Amendment 2	Rationale
Synopsis: Location	Multinational, including North and South America, Europe, and Australia	Multinational, including North and South America, **South Africa, and** Europe ~~**and Australia**~~	To update regions where study is conducted.
Title Page: Sponsor	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland	Myovant Sciences GmbH **Viaduktstrasse 8** **4051** Basel Switzerland	Sponsor address updated.
Synopsis: Secondary Efficacy Objectives Section 3 Study Objective and Endpoints	• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: … None. None.	• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: … o Impact of uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient Global Assessment (PGA) for	To add a new secondary efficacy objective related to the impact of uterine fibroids on symptoms, activities, and QOL and to add a patient global assessment for function and symptoms. Clarified the instrument to be used for assessing impact of heavy menstrual bleeding on social, leisure and physical activities.

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	o Impact of heavy menstrual bleeding on social, leisure, and physical activities;	function and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities **as measured by the Menorrhagia Impact Questionnaire (MIQ)**; o **Pain associated with uterine fibroids;**	
Synopsis: Safety Objectives Section 3 Study Objective and Endpoints	None. None.	• To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids.	Objectives related to BMD analysis at 12 weeks and analysis of vasomotor symptoms are added
Synopsis: Study Design Section 4.1 Overall Study Design Section 5.1 Treatments Administered	During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks.	During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. **The last dose of study drug for the Randomized Treatment Period will be taken on the immediate day prior to the Week 24 visit.**	To allow transition into the extension study (MVT-601-3003). Week 24 visit will be the first day of MVT-601-3003. Patients who qualify for and provide informed consent to enroll in MVT-601-3003 will take the first dose of open label study drug at Week 24.
Synopsis: Study Design	All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients	During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken on the day immediately before to	Added additional text to provide details on the transition of patients into the extension study (MVT601-3003). The Week 24 visit will be the first day of the

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	who do not enroll into the extension study will have a follow-up visit to assess safety approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).	the Week 24 visit. Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).	extension study. Also added additional follow-up activities for patients not enrolling into the extension study.
Synopsis: Inclusion Criteria Section 4.3.1 Inclusion Criteria Section 4.7 Contraception/ Pregnancy Avoidance	8. Agrees to use two forms of nonhormonal contraception (dual contraception, as described in Section 4.7) consistently during the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she: …	8. Agrees to use **~~two forms of nonhormonal~~** contraception **during the study and for 30 days following the last dose of study drug. Specifically agrees to use** nonhormonal contraception, **~~(dual contraception~~** as described in Section 4.7 consistently during the Screening period, and the Randomized Treatment Period **and either nonhormonal or oral contraceptives after return of menses following treatment**	To specify use of contraceptives for 30 days following treatment. Also removed the requirement for dual nonhormonal contraception as spermicide is not available in all countries.

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		discontinuation. However, the patient is not required to use ~~**dual**~~ **specified non-hormonal** contraception if she: … c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of ~~**dual**~~ non-hormonal contraception **as described in Section 4.7**;	
Synopsis: Inclusion Criteria Section 4.3.1 Inclusion Criteria	9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded;	9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: ~~**polyps < 2.0 cm by ultrasound are not excluded;**~~ **Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or <2 cm are eligible;**	To provide clarity.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	4. Has a weight that exceeds the weight limit of the DXA scanner;	4. Has a weight that exceeds the weight limit of the DXA scanner **or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);**	Adds exclusion for any other condition that would interfere with obtaining an interpretable DXA scan.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	6. … A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;	6. … ~~**A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;**~~ **Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;**	To provide clarity.
Synopsis:	13. Has any of the following	13. Has any of the following	Added to exclude

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Exclusion Criteria Section 4.3.2 Exclusion Criteria	clinical laboratory abnormalities at any screening visit: … … d. None. e. None.	clinical laboratory abnormalities at any screening visit: … d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN); e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN)	patients with conditions that would result in abnormal calcium and phosphorus levels.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	14. Has clinically significant cardiovascular disease including: … e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec; g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;	14. Has clinically significant cardiovascular disease including: … e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec **on the Screening visit or Baseline Day 1 ECG;** g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg ~~**on 2 repeat measures at least 15 minutes apart**~~ or diastolic blood pressure > 100 mmHg **on 2 repeat measures at least 15 minutes apart** at any screening visit or the Baseline Day 1 visit;	To provide clarification on visits for the exclusion criteria. To clarify that both systolic and diastolic blood pressure criteria must be demonstrated on 2 repeat measures.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	16. Has a history of clinically significant condition(s) including, but not limited to the following: … a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded); None.	16. Has a history of clinically significant condition(s) including, but not limited to the following: … a. Untreated thyroid dysfunction ~~**or palpable thyroid abnormality**~~ (patients with adequately treated hypothyroidism who are stable on medication are not excluded); d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;	Deleted as redundant. Untreated palpable abnormality would generally fall under untreated thyroid dysfunction. To add an exclusion criterion for systemic autoimmune disease.
Synopsis: Exclusion	17. Is currently pregnant or lactating, or intends to become	17. Is currently pregnant or lactating, or intends to become	To clarify the

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Criteria Section 4.3.2 Exclusion Criteria	pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;	pregnant **during the study period through 1 month after the last dose of study drug** or **intends** to donate ova during the study period or within 2 months after the last dose of study drug;	pregnancy window.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.	23. Is inappropriate for participation in this study ~~**for other reasons**~~ **because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements,**~~-~~as determined by the investigator, sub-investigator, or medical monitor;	To explain circumstances and provide examples when a potential patient would be inappropriate for participation in the study.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	None.	24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.	Added new exclusion criteria to avoid confounding the assessment of hemoglobin.
Synopsis: Secondary Efficacy Endpoints Section 3 Study Objective and Endpoints Section 9.3.2 Statistical Considerations and Data Analyses	The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: … • Proportion of women who achieve amenorrhea over the last 35days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by the alkaline hematin method; None. None.	The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: … • Proportion of women who achieve amenorrhea over the last 35 days of treatment ~~**as measured by the alkaline hematin method;**~~ • None. • Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11; • Change from Baseline to	Time to amenorrhea Endpoint removed due to redundancy. Presenting the amenorrhea rate using a proportion versus a cumulative Kaplan-Meier probability is preferred since it is more consistent with method used for the primary responder endpoint analysis. Added secondary endpoints related to UFS-QOL and PGA for function and symptoms to address the added secondary objectives.

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	None. None. None. None. None. None.	Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to Week 24;	
Synopsis: Safety Endpoints Section 3 Study Objective and Endpoints	None. • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA;	• Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week~~s~~ **~~12 and~~** 24 in bone mineral density at the **lumbar** spine (~~average of~~ L1-L4), total hip, and femoral neck as assessed by DXA;	Endpoint for assessment of bone mineral density at Week 12 is pre-specified as a separate endpoint with comparison between Group A and Group B. This endpoint will support inclusion of add-back therapy in the treatment regimen.
Synopsis: Exploratory Endpoints Section 3 Study Objective and Endpoints Section 9.6 Exploratory Analyses	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively;	None.	Exploratory endpoints related to UFS-QOL are removed, and secondary endpoints related to assessments of certain components UFS-QOL are added.
Section 1.1	Visit window timing (days)	Visit window timing (days)	Visit window

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Schedule of Activities Table 1-1	Week 24 (or Early Termination of Study Drug) ± 10	Week 24 (or Early Termination of Study Drug): ~~± 10~~ **-10/+20**	expanded to allow transition of eligible patients into open label extension study MVT-601-3003 without interruption.
	None.	PGA for function PGA for symptoms	Added new assessments in line with new secondary efficacy endpoints.
	Treatment Compliance	Treatment Compliance **and Study Drug Accountability**	Updated to clarify the assessment.
	Week 4 through Week 24 None.	Week 4 through Week 24 Treatment compliance and drug accountability	Added additional assessments for treatment compliance and urinalysis at week 24.
	Week 24 (or Early Termination of Study Drug) None.	Week 24 (or Early Termination of Study Drug) Urinalysis	Added additional assessments for follow up visit for patients who do not roll-over to the extension study.
	Follow-up None.	Follow-up Temperature collection, pregnancy test, status of menstruation recovery	
Section 1.1 Schedule of Activities Table 1-1 footnotes	d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose pharmacodynamic sample, pregnancy and urinalysis test samples prior to first dose of study drug. The patient must complete MIQ, UFS-QoL, and EQ-5D questionnaires prior other study procedures and prior to first dose of study drug.	d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. **The following procedures must be completed prior to randomization: urine pregnancy, vital signs, waist circumference, weight, temperature, complete physical examination, visual acuity assessment,12-lead ECG, and review of eligibility criteria.** Collect clinical laboratory **sample**, PK sample**,** ~~**pre-dose**~~ pharmacodynamic sample, ~~**pregnancy**~~ and urinalysis prior to first dose of study drug. ~~**The patient must**~~ **Whenever possible,** complete MIQ, UFS-QOL, **PGA for symptoms and PGA for function,** and EQ-5D-**5L** ~~**questionnaires prior other**~~	To clarify order of assessments during baseline Day 1 visit.

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		~~**study procedures and**~~ prior to the first dose of study drug.	
	e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.	e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit. **The last dose of study drug in the Randomized Treatment Period will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.**	To provide clarity on definition of Week 24 visit and when the last dose is taken.
	h. Visual acuity must be assessed with the study eye chart. The patient should wear any prescription glasses or contacts during the assessment.	h. Presenting visual acuity must be assessed with the supplied study eye chart. **If the** patient **uses corrective lenses, she** should wear ~~**any**~~**her usual** prescription glasses **or contact lenses** during the assessment, **and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions. See Study Reference Manual for additional instructions on visual acuity testing and see Section 6.8.2.8 for overall guidance including follow-up.**	To provide guidance on visual acuity examination and follow-up.
Section 1.1 Schedule of Activities Table 1-1 footnote i Section 6.2.1 Screening 1 Visit Section 6.8.2.3 Physical and Gynecologic Exams	Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit.	Papanicolaou test must be conducted for women without a test result within ~~**6 months**~~ **2 years** prior to the Screening 1 visit.	Window for Papanicolaou test expanded to approach the guidelines for cervical cancer screening.

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Section 1.1 Schedule of Activities Table 1-1 footnote j	…Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests.	…Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests. **In addition to clinical chemistries and a complete blood count, include thyroid-stimulating hormone at Screening 1. Screening laboratory tests may be repeated during the screening period once, if necessary, at the investigator's discretion. Additional re-testing requires the approval of the medical monitor. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.**	To provide clarification on laboratory tests: to indicate thyroid-stimulating hormone testing at Screening 1, repeats of screening tests, and testing for iron and ferritin in patients with microcytic anemia.
Section 1.1 Schedule of Activities Table 1-1 footnote k	…In addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, Vitamin D, iron, ferritin, and hemoglobin A1c.	…In addition to clinical chemistries and a complete blood count, include a lipid profile, ~~**levels of parathyroid hormone, thyroid-stimulating hormone,**~~ prolactin, Vitamin D, ~~**iron, ferritin,**~~ and hemoglobin A1c.	Parathyroid hormone testing is removed (patients with abnormal calcium and phosphorus will be excluded). Thyroid stimulating hormone level will be obtained at Screening 1.
Section 1.1 Schedule of Activities Table 1-1 footnotes m, n	…Administer study drug after PK and pharmacodynamics sample collections are complete…	…Administer study drug after PK and pharmacodynamics sample collections are complete **(Study drug is not administered at Week 24 Visit; for patients proceeding into the extension study, refer to protocol for study MVT-601-3003).**	Added note at end of footnotes for PK and PK samples clarifying that no study drug is administered at the Week 24 visit
Section 1.1 Schedule of Activities Table 1-1 footnote o Section 6.8.1.11 Pharmacogenomics Sample	Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected.	Pharmacogenomics sample **(unless precluded by local law or regulations)**: a separate pharmacogenomics consent is required before this sample may be collected.	Added note that pharmacogenomics sample will not be obtained if precluded by local laws or regulations

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Collection			
Section 1.1 Schedule of Activities Table 1-1 footnotes	None.	w. Patients not proceeding to the extension study who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will be followed and will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination visit (see Section 6.7). The repeat biopsy will be submitted to the central laboratory.	Added new footnote to provide guidance on scheduling DXA assessments and follow-up for patients not entering the extension study.
	None.	x. Schedule DXA as early as possible within the Week 24/Early Termination visit window. Patients not proceeding to the extension study who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo another DXA scan at 6 (± 1) months after the Week 24/Early Termination visit scan to evaluate recovery and will be contacted about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.	Added new footnote for follow-up procedures for abnormal endometrial biopsy for patients not proceeding into the extension.
	None.	y. Patient will enter responses in a paper questionnaire at the site.	Added new footnote that PGAs for functions and symptoms are completed as a paper questionnaire.
	None.	z. The patient should be asked to bring all study drug to the clinic at each visit. Please refer to section 5.8.	Clarification.
Section 2.2.4.4 Clinical Studies in Women with Uterine Fibroids or	The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to	Adverse drug reactions associated with relugolix in women with uterine fibroids or endometriosis include hot flush, headache, hyperhidrosis and bone	Updated for consistency with the Investigator Brochure.

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Endometriosis and Men with Prostate Cancer	relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.	density decreased. Adverse drug reactions associated with relugolix in men with prostate cancer include hot flush, fatigue, arthralgia, nausea, weight increased, gynecomastia and night sweats.	
Section 4.1 Overall Study Design Figure 4-1	Open-Label Extension Study (Eligible Patients) 24 Weeks	Open-Label Extension Study (Eligible Patients) **28** Weeks	Study schematic updated to indicate the open-label extension is 28 weeks instead of 24 weeks
Section 4.1 Overall Study Design Figure 4-2 Figure legend	Bottom scenario: … • Patients whose first screening cycle MBL is < 80 mL and whose second screening cycle menstrual blood loss is > 160 mL will follow the bottom scenario visit schedule Additional Scenarios (not depicted): … • … If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule.	Bottom scenario: … None. Additional Scenarios (not depicted): … • … If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule, **and the patient does not need to collect menstrual blood loss for another cycle.**	Clarification Schematic of Screening Visit Scenarios is updated to indicate that for patient with MBL ≥ 160 mL do not need to collect menstrual blood loss for another cycle.

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Section 4.6 Removal of Patients from Therapy	• Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements.	• Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements. **This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; missing multiple study visits; and persistent (> 2 consecutive months) with < 50% of the required number of days of eDiary completion;** • **Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment;**	To provide definition of gross non-compliance. Add criteria for withdrawal from treatment for patient whose treatment assignment has been unblinded to harmonize with Section 5.7.
Section 4.7 Contraception/ Pregnancy Avoidance	In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply: … The only acceptable methods of dual contraception are: • Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);	In this study, medications and devices containing hormones **for contraception** are excluded, and patients must agree to use ~~**two forms of**~~non-hormonal contraception ~~**(dual contraception)**~~ **throughout the study, including through 30 days following the last dose of study drug**, unless any of the following apply: … The only acceptable methods of ~~**dual**~~ contraception **for those for whom one of the above methods do not apply** are: • Condom **(male or female condom)** with **or without** spermicide (cream, spray, foam, gel, suppository or polymer film);	As the common spermicide, nonoxynol-9 (N-9), is no longer approved in several countries participating in the study and other effective spermicides are not readily available in those countries, the protocol-specified contraceptive methods were reviewed and the use of a condom (male or female) with or without spermicide permitted.

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Section 5.1 Treatments Administered	Each patient will be instructed to take one tablet and one capsule per day.	Each patient will be instructed to take one tablet and one capsule per day. **The last dose of study drug will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.**	Added text to clarify last dose due to transition into extension study (see above).
Section 5.4 Directions for Administration	The study treatment should be taken in the fasted state (other than water) in the morning, at least 1 hour before breakfast. … Patients should take any oral iron supplementation with meals.	The study treatment should be taken in the fasted state (other than water**, tea, or coffee**) in the morning, at least 1 hour before breakfast. … None.	Definition of fasted state for drug administration is clarified to include tea or coffee. Restriction to take iron with meals is removed.
Section 5.5 Dose Reduction/Dose Administration Section 7.1.1 Adverse Event	…Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).	**…~~Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event.~~** Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).	Text removed as it is the investigator's responsibility to determine appropriate management of study drug in a setting of an adverse event
Section 5.6 Storage, Packaging, and Labeling	Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 35°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee).	Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to **~~35°C~~ 25°C** with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). **Study drug should be stored protected from light.**	Modified to be consistent with study drug labeling.
Section 5.7 Blinding	Investigators will have direct access to a given patient's individual study treatment, however, the investigator should make every effort to first contact the medical monitor or appropriate study personnel to discuss options **before** unblinding the patient's treatment assignment.	**~~Investigators will have~~The decision to unblind a patient's treatment assignment in an emergency situation resides with the investigator who has** direct access to **unblind** a patient's individual study treatment; however, the investigator should **~~make every effort~~**attempt to contact the medical monitor or appropriate study personnel to discuss	To provide clarification that the decision to break the treatment code in emergency situation resides with the investigator.

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		options before unblinding the patient's treatment assignment **unless the urgency of the medical situation precludes this.**	
Section 5.8 Study Drug Accountability and Treatment Compliance	If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%) it may be appropriate to withdraw the patient from the study.	If a patient is persistently noncompliant with the study treatment **~~(ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%)~~** it may be appropriate to withdraw the patient from the study **(see Section 4.6).**	Revised to align with criteria for removal from therapy.
Section 5.10.1 Prohibited Medications Table 5-3	Anti-convulsant drugs (specified) Examples phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone Progestins Examples dienogest norethindrone medroxyprogesterone Estrogen Examples estradiol valerate conjugated estrogens Oral Contraceptives Examples combined or progestin only	Anti-convulsant drugs (specified) Examples phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone **Note: All other anticonvulsants are allowed** Progestins **and progestin implants.** Examples dienogest norethindrone medroxyprogesterone **cyproterone** **etonogestrel** Estrogen Examples estradiol valerate conjugated estrogens **ethinyl estradiol** **Hormonal ~~oral~~ contraceptive patches and vaginal rings** Examples combined or progestin only **Nuva Ring**	Added clarification that other anticonvulsants not listed are allowed. To include additional examples of prohibited medications. To include additional examples of prohibited medications. To include additional examples of prohibited medications.
Section 5.10.1 Prohibited Medications	Bone Agents Window/Comments No prior use if used for reduced	Bone Agents Window/Comments No prior use if used for reduced	Provide a specific clarification that Calcium and vitamin

Item; Section(s)	Protocol Amendment 1	Amendment 2	Rationale
Table 5-3	bone mineral density	bone mineral density **Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.**	D are allowed.
Section 5.10.1 Prohibited Medications Table 5-3	P-glycoprotein Inducers Examples carbamazepine rifampin St. John's wort	P-glycoprotein Inducers Examples **avasimibe** carbamazepine **phenytoin** rifampin St. John's wort **tipranavir/ritonavir**	To include additional examples of prohibited medications. Clarify when short term use of these Pgp inducers can be allowed in study.
Section 5.10.1 Prohibited Medications Table 5-3	Moderate and Strong P glycoprotein Inhibitors Examples None. Footnotes None.	Moderate and Strong P glycoprotein Inhibitors Examples amiodarone, atazanavir[f], azithromycin[a], captopril[b], carvedilol[g], clarithromycin[a], cobicistat[f], conivaptan, cyclosporin[c], diltiazem, dronedarone, erythromycin[a], felodipine[d], itraconazole[e], ketoconazole[e], lopinavir/ritonavir[f], quercetin, quinidine,,ranolazine, ticagrelort[g], verapamil Footnotes **a. Roxithromycin is allowed** **b. All other angiotensin converting enzyme inhibitors are allowed** **c. Tacrolimus is allowed** **d. Amlodipine and nifedipine are allowed** **e. Fluconazole is allowed** **f. Integrase inhibitors are allowed** **g. Metoprolol and atenolol are permitted**	To include additional examples of prohibited medications. Clarify when short term use of these Pgp inhibitors can be allowed in study.
Section 6.2.1 Screening Visit 1	The order of procedures should be as follows. …	The order of procedures should be as follows. …	Added new text to provide clarification

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	None. None.	• Complete physical examination and visual acuity assessment • Clinical laboratory tests, including TSH, urinalysis	for the order of procedures.
Section 5.10.2.2 Iron Therapy Section 6.2.1 Screening Visit 1 Section 6.2.2 Screening Visit 2 Section 6.8.2.4 Clinical Laboratory Samples	None. If the hemoglobin is < 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be obtained as an unscheduled test	**If the hemoglobin is < 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.** If the hemoglobin is < 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be **reported through the central lab ~~obtained as an unscheduled test~~.**	Added new text to provide guidance on laboratory diagnosis and management of iron deficiency anemia. For Section 6.2.2 Clarified that iron and ferritin are be reflex labs that will be reported trough central laboratory.
Section 6.2.6 Retesting	None.	Screening laboratory tests may be repeated once during the Screening period, if necessary, at the investigator's discretion. For laboratory-based entry criteria, the most recent value will be used to determine eligibility. Additional laboratory retesting requires the approval of the medical monitor. Retesting of other procedures (except once, as required, due to technical or logistical issues such as an inadequate sample) also require approval of the medical monitor.	New section added to allow single repeat of screening laboratory tests.
Section 6.6 Additional Safety Follow-Up Procedures	None.	For patients not continuing into the extension study (MVT 601-3003), additional safety procedures are required in some circumstances as described below. These procedures will be performed during unscheduled visits. • Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses	New section added to provide guidance for additional safety follow up procedures for patients who do not proceed into extension study.

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		has resumed and questioned about factors that may affect resumption of menses. • Patients with endometrial biopsy findings of endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings during through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory. In addition, patients with endometrial hyperplasia with atypia will be evaluated and managed, as needed, by a gynecologist. • Patients who have had a bone mineral density loss of > 2% at the lumbar spine (average of L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scanning. The follow-up DXA scan will be submitted for central reading.	
Section 6.8.1.2 Transvaginal and Transabdominal Ultrasound	None.	Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone or when endometrium cannot be evaluated or when	Added clarification regarding use of saline or gel contrast for ultrasound.

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		there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.). If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24	
Section 6.8.1.5 Patient Diary	The eDiary data will be reviewed by the investigator to identify any potential adverse events.	The eDiary data will be reviewed by the **study staff.** ~~**investigator to identify any potential adverse events**~~	To ensure consistency with section 7.2 of the protocol stating that eDiary entries will be reviewed by study site personnel.
Section 6.8.1.9 Patient Global Assessment for Symptoms and Patient Global Assessment for Function	None.	These simple questions are used by the patient to qualitatively describe severity of symptoms or effects on function (PGA) (see Appendix 6) on a schedule described in the Schedule of Activities (Section 1.1). With the exception of Baseline Day 1 (see Section 1.1), patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (Section 1.1). With the exception of Baseline Day 1, patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site.	New section added to describe assessments for the newly add PGA secondary objectives.

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Section 6.8.1.10 Status of Menstruation Recovery	After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued.	None.	Menstruation recovery follow up outlined in Section 6.6.
Section 6.8.2.3 Physical and Gynecologic Exams	Visual acuity will be checked at the beginning and end of the study by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment.	None.	Visual acuity assessment instructions moved to a new section.
Section 6.8.2.4 Clinical Laboratory Samples **Table 6-1**	Chemistry Creatinine Kinase Hormones Intact Parathyroid Hormone	Chemistry ~~**Creatinine Kinase**~~ Hormones ~~**Intact Parathyroid Hormone**~~	Parathyroid hormone testing is removed (patients with abnormal calcium and phosphorus will be excluded). "Creatinine kinase" Typographical error removed.
Section 6.8.2.6 Endometrial Biopsy	An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A pipelle should be used to obtain the specimen. A second biopsy is to be performed at the Week 24 visit. The biopsies will be read centrally.	An endometrial biopsy will be obtained using an endometrial suction curette (eg, Pipelle®) and submitted to the central laboratory for reading. If the biopsy is inadequate for diagnosis at either Screening or at Week 24, it should be repeated and sample submitted to the central laboratory. If the second specimen is also inadequate for diagnosis at Screening, the patient is not eligible for the study.	To provide clarification and details for endometrial biopsy.
Section 6.8.2.7 Bone Mineral Density	Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient.	Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient). **The scans will be read by the central radiology laboratory in accordance with the imaging charter.**	Added clarification of central reading.
Section 6.8.2.7 Bone Mineral Density	The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section	None.	Deleted details on analysis of bone mineral density. This info will be

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	1.1): bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.		provided in the SAP.
Section 6.8.2.7 Bone Mineral Density	Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the sties assessed during the study. In this case, repeat scan may be required for confirmation of the results, and it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.	Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the **anatomical** sites assessed during the study. In this case, ~~**repeat scan may be required for confirmation of the results, and**~~ **it is at the investigator's discretion to consider the patient's status and determine future management.** Detailed instructions for ~~**bone mineral density monitoring DXA scanning**~~ will be provided in the Study Reference Manual. **Please see Section 6.6 for follow-up of patients who are not continuing into the extension study (MVT-601-3003) and whose bone mineral density has decreased by > 2% at the lumbar spine (L1-L4) or total hip at the Week 24/Early Termination visit relative to Baseline.**	Further specified follow-up measures for observed bone mineral density loss.
Section 6.8.2.8 Visual Acuity	None.	Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see Study Reference Manual for additional details).	New section created to provide additional details and to align with other studies with relugolix.

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		Patients whose presenting visual acuity score is 90 or lower at the Baseline visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history. Patients whose presenting visual acuity score at Week 24 /Early termination has decreased by 10 or more points from Baseline should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.	
Section 7.1.1 Adverse Event	Events that do not meet the definition of an adverse event include: … • None.	Events that do not meet the definition of an adverse event include: … • Events of heavy menstrual bleeding, as heavy menstrual bleeding is quantified as an efficacy endpoint, unless the event meets seriousness criteria.	As heavy menstrual bleeding is being assessed as an efficacy endpoint, added it to list of events that do not meet definition of adverse event. Also clarified that would be reportable as an adverse event if met the criteria for seriousness.
Section 7.6 Serious Adverse Event Reporting	Table providing details to send completed Safety Report Forms to PRA Safety & Risk Management	Table updated to send completed Safety Report Forms to **QuintilesIMS**	Updated Contact info for reporting Serious Adverse events. Updates to e-mail and phone number are also included in this section.
Section 7.10 Benefit/Risk Assessment Table 7-2	<u>Impact on Eligibility</u> Exclusion criteria for a history of osteoporosis, osteopenia, metabolic bone disease, …	<u>Impact on Eligibility</u> Exclusion criteria for a history of osteoporosis, ~~**osteopenia**~~, metabolic bone disease, …	Osteopenia is not an exclusion criterion in this study.
Section 7.10 Benefit/Risk Assessment Table 7-2	Hepatic Enzymes	Hepatic Enzyme **Increase**	Updated naming of this potential risk, matching IB nomenclature

Item; Section(s)	Protocol Amendment 1	Amendment 2	Rationale
Section 9.2 Statistical Considerations and Data Analyses	The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations.	The Per-Protocol Population will consist of those members of the ITT Population who have no **relevant** major protocol violations, **defined as a subset of all major protocol violations (details will be provided in the statistical analysis plan).**	Clarification.
Section 9.3.2 Statistical Considerations and Data Analyses	For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume and time to amenorrhea, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients for whom the first time at which menstrual blood loss of <80 mL AND at least a 50% reduction from baseline is achieved is during a cycle when no feminine products were returned due to amenorrhea absence of a menstrual period, the most recent menstruation stop date will be used. … Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline.	For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume ~~**and time to amenorrhea**~~, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. ~~**Patients for whom the first time at which menstrual blood loss of <80 mL AND at least a 50% reduction from baseline is achieved is during a cycle when no feminine products were returned due to amenorrhea absence of a menstrual period, the most recent menstruation stop date will be used.**~~ … Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, **UFS-QOL score, PGA for function and symptoms, MIQ Score,** Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline.	Changes made to ensure consistency with changes in secondary efficacy endpoints.
Section 9.4 Safety Analyses	None.	To support the inclusion of add-back therapy in the treatment regimen, the safety endpoint of mean percent change from Baseline in bone mineral density lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal comparison of	To provide clarification on analysis plans for bone mineral density which includes pooling of data across the two replicate studies.

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		Group A versus Group B (see details in the joint statistical analysis plan).	
Appendix 6 Patient Global Assessments	None.	Patient Global Assessment (for function) How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? 1. No limitation at all 2. Mild limitation 3. Moderate limitation 4. Quite a bit of limitation 5. Extreme limitation Patient Global Assessment (for symptoms) How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? 1. Not severe 2. Mildly severe 3. Moderately severe 4. Very severe 5. Extremely severe	To support secondary objectives.

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 08-FEB-2017 Amendment 2: 18-SEP-2017

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3001

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

18- Sep- 2017
Date

18- Sep 2017
Date

18 Sept 2017
Date

18 Sep 2017
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menorrhagia Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart
PD	Pharmacodynamics
PGA	Patient Global Assessment

Term	Explanation
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QOL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3001
Location	Multinational, including North and South America, South Africa, and Europe
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	Primary Efficacy Objective • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. Secondary Efficacy Objectives • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient Global Assessment (PGA) for function and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks; • To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.
	Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures (EQ-5D-5L).

Study Design

This study is an international phase 3, randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal ultrasound (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during 1 cycle during the screening period. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during Screening must be treated with oral or parenteral iron replacement therapy. Between the

Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. Another transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24, followed by a repeat endometrial biopsy. Patients will have paired baseline and end-of-treatment endometrial biopsies, independent of ultrasound results. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken on the day immediately before to the Week 24 visit.

Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).

Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at

least one of the following criteria:

a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or

b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone;

5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use contraception during the study and for 30 days following the last dose of study drug. Specifically agrees to use non-hormonal contraception, as described in Section 4.7 consistently during the Screening period and the Randomized Treatment Period and either nonhormonal or oral contraceptives after return of menses following treatment discontinuation. However, the patient is not required to use specified non-hormonal contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described in Section 4.7;
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or < 2 cm are eligible;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study.

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);

2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline

Day 1 visit);

b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);

c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;

d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);

e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);

14. Has clinically significant cardiovascular disease including:

a. Prior history of myocardial infarction;

b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);

c. History of congestive heart failure;

d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);

e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the Screening visit or Baseline Day 1 ECG;

f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;

g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on 2 repeat measures at least 15 minutes apart at any screening visit or the Baseline Day 1 visit;

h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening or Baseline Day 1 ECG electrocardiogram unless judged by the investigator to be due to physical fitness;

15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;

16. Has a history of clinically significant condition(s) including, but not limited to the following:

a. Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who are stable on medication are not excluded);

b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;

c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;

d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic

syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted; 17. Is currently pregnant or lactating, or intends to become pregnant during the study period through 1 month after the last dose of study drug or intends to donate ova during the study period or within 2 months after the last dose of study drug; 18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary window periods for these medications are also described therein); 19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form); 21. Has participated in a previous clinical study that included the use of relugolix; 22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling); 23. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor; 24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.	
Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color.

Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. <u>Primary Efficacy Endpoint</u> • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11; • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.

	Safety Endpoints • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.
	Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations ($C\tau$) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.
	Exploratory Endpoint • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of 260 (130

patients in each of the relugolix and placebo arms) will provide > 99% power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3001

	SCREENING PERIOD[a]				**RANDOMIZED TREATMENT PERIOD**								**SAFETY FOLLOW-UP**
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Un-scheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)		Within 5 (+2) days after completion of Screening 1 menses	Within ≤ 15 days after Screening 2 visit	Within 5 (+2) days after completion of 2nd Screening menses	Within 7 days of the start of menses	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**-10/+20**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X[e]	X
Waist Circumference					X								
Height	X												
Weight	X				X						X	X[e]	X
Temperature	X				X						X	X[e]	X
Adverse Event Collection[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity[h]					X						X	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD								SAFETY FOLLOW-UP
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Complete Physical excluding GYN Examination	X				X						X		
GYN Examination with Pap Test, if applicable	X[i]												
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X[e]	X
12-Lead Electrocardiogram			X		X			X			X	X[e]	X
Clinical Laboratory Tests[j]	X	X			X[k]	X	X	X	X	X	X[l]	X[e]	X
PK Sample[m]					X	X		X			X	X[e]	
PD Sample[n]					X	X		X			X	X[e]	X
Daily Study Drug Administration					X (Day 1 through day *immediately prior* to Week 24/Early Termination visit)							X[e]	
Administer Dose of Study Drug in Clinic					X	X	X	X	X	X		X[e]	
PGx Sample[o]					X							X[e]	
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X	X[e]	X
Urinalysis	X				X						X	X[e]	
Mammogram[p]	schedule	X											
Transvaginal Ultrasound (with or without Transabdominal Ultrasound)[q]	X										X[s]	X[e]	
Endometrial Biopsy[r]	X										X[s, w]	X[e]	
Bone Densitometry[t]	schedule	X						X			X[s, x]	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD								SAFETY FOLLOW-UP
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Randomization					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X		X[e]	
Dispense Study Treatment					X	X	X	X	X	X		X[e]	
Patient paper diary/ eDiary[u]	X	X	X	X	X	X	X	X	X	X	X	X[e]	
Feminine Product Collection and Venous Blood Sample[v]		X		X		X	X	X	X	X	X	X[e]	
MIQ					X	X	X	X	X	X	X	X[e]	
UFS-QOL					X			X			X	X[e]	
EQ-5D-5L					X						X	X[e]	
PGA for function[y]					X	X	X	X	X	X	X	X[e]	
PGA for symptoms[y]					X	X	X	X	X	X	X	X[e]	
Treatment Compliance and Study Drug Accountability[z]						X	X	X	X	X	X	X[e]	
Status of Menstruation Recovery													X

Notes:

Abbreviations: DXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; GYN, gynecology; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGA, Patient Global Assessment; PGx, pharmacogenomics; PK, pharmacokinetics; UFS-QOL, Uterine Fibroid Symptom and Health-Related Quality of Life.

For patients who are re-screening, please see Section 6.2.6 for abbreviated screening procedures.

a. The screening period should be initiated after the informed consent form is signed and any exclusionary windows for prohibited medications has been confirmed.
b. Visit to occur within 5 (+2) days of the completion of menses. Visit 4 should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.
c. Visit to occur within ≤ 15 days after Screening 2 visit; eDiary dispensation must occur at least 7 days prior to Baseline Day 1. The alkaline hematin menstrual blood loss collection may be repeated once at the discretion of the investigator if one menstrual cycle does not meet menstrual blood loss criteria thought to be due to inadequate collection for a highly motivated patient.

d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. The following procedures must be completed prior to randomization: urine pregnancy, vital signs, waist circumference, weight, temperature, complete physical examination, visual acuity assessment,12-lead ECG, and review of eligibility criteria. Collect clinical laboratory sample, PK sample, pharmacodynamic sample, and urinalysis prior to first dose of study drug. Whenever possible, complete MIQ, UFS-QOL, PGA for symptoms and PGA for function, and EQ-5D-5L prior to the first dose of study drug.
e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit. The last dose of study drug in the Randomized Treatment Period will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit is defined as the last day on which a Week 24 visit procedure is conducted.
f. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003) and/or terminate early from the study, a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~30 days after an Early Termination visit).
g. Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure) through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first.
h. Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100; continue as far as the patient can go per the testing instructions. See Study Reference Manual for additional instructions on visual acuity testing and see Section 6.8.2.8 for overall guidance including follow-up.
i. Papanicolaou test must be conducted for women without a test result within 2 years prior to the Screening 1 visit. The specimen should be submitted to the central laboratory during screening. Another test should be performed for inadequate or false-positive results and be submitted to the central laboratory.
j. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests. In addition to clinical chemistries and a complete blood count, include thyroid-stimulating hormone at Screening 1. Screening laboratory tests may be repeated during the screening period once, if necessary, at the investigator's discretion. Additional re-testing requires the approval of the medical monitor. If the hemoglobin is $\leq$ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.
k. At the Baseline Day 1 visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, prolactin, Vitamin D, and hemoglobin A1c. An additional sample will be collected at this visit in all patients and stored for possible future testing for presence of hepatitis A, B, and C if required per request from medical monitor to assess etiology of liver test abnormalities.
l. At the Week 24 visit or Early Termination visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.
m. Pharmacokinetics samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics sample collections are complete (Study drug is not administered at Week 24 Visit; for patients proceeding into the extension study, refer to protocol for study MVT-601-3003).
n. Pharmacodynamic samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Early Termination and Follow Up visits). Study drug is not administered at the Week 24 Visit for patients proceeding into the extension study (refer to protocol for study MVT-601-3003).

o. Pharmacogenomics sample (unless precluded by local law or regulations): a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive)
p. Patients ≥ 39 years of age at the time of the anticipated Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period; if not, schedule at the Screening 1 visit.
q. Transvaginal ultrasound with or without transabdominal ultrasound must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm. Results must be submitted to and uterine fibroid criteria confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is required. See inclusion criterion #5 and exclusion criterion #1 for guidance as to when to perform a transabdominal ultrasound and saline or gel contrast. If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24.
r. Obtain sample with an endometrial suction curette (eg, Pipelle®). Endometrial biopsy is performed at Screening 1 visit and Week 24 Visit and submitted to the central laboratory. See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis.
s. Procedure not required at the Early Termination Visit in patients whose last dose of study drug was during Week 6 or earlier. The procedure may be done if it will aid in the evaluation of an ongoing adverse event.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results will be available prior to randomization. Schedule the test at or shortly after the Screening 1 visit. Bone densitometry should be completed prior to the Screening 3 visit and as early as possible to ensure results are available prior to randomization.
u. Patient paper diary: Patients enter diary information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit. Patient eDiary: Ensure that eDiary data collection begins at least 7 days prior to Day 1. Patients enter eDiary information on a daily basis for their compliance with study treatment starting at Baseline/Day 1, menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening 3 visit through Week 24 or Early Termination.
v. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.
w. Patients not proceeding to the extension study who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will be followed and will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination visit (see Section 6.7). The repeat biopsy will be submitted to the central laboratory.
x. Schedule DXA as early as possible within the Week 24/Early Termination visit window. Patients not proceeding to the extension study who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo another DXA scan at 6 (± 1) months after the Week 24/Early Termination visit scan to evaluate recovery and will be contacted about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.
y. Patient will enter responses in a paper questionnaire at the site.
z. The patient should be asked to bring all study drug to the clinic at each visit. Please refer to Section 5.8.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which

are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotropin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies (including 1 in women with uterine fibroids and 1 in women with endometriosis) have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least 1 dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations of estradiol in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

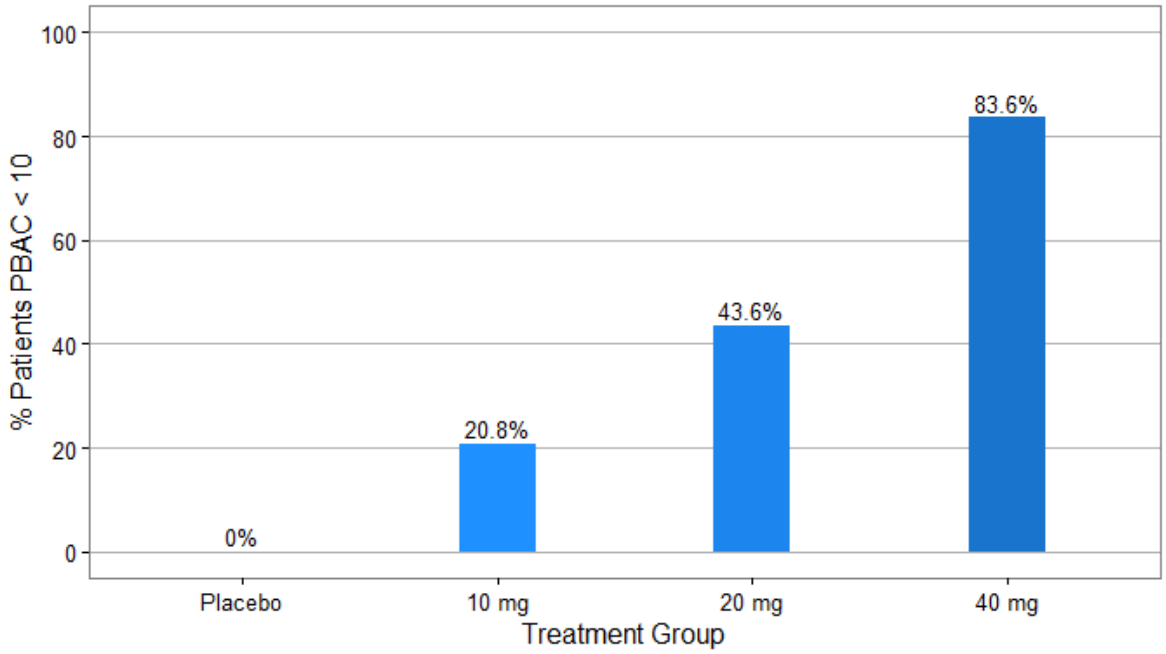
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 19%. The exposure of relugolix is increased by inhibitors

of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 final analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤ 50 ng/dL) and maintained these levels through at least 24 weeks. These 24-week data were comparable to testosterone levels achieved by leuprolide 22.5 mg administered by injection every 3 months. Study C27003 also demonstrated rapid and sustained suppression of testosterone levels by relugolix for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. Adverse drug reactions associated with relugolix in women with uterine fibroids or endometriosis include hot flush, headache, hyperhidrosis and bone density decreased. Adverse drug reactions associated with relugolix in men with prostate cancer include hot flush, fatigue, arthralgia, nausea, weight increased, gynecomastia and night sweats.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
Primary Efficacy	
• To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of uterine fibroids on symptoms, activities and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient Global Assessment (PGA) for function	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin

Objective(s)	Endpoint(s)
and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.	below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11; • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of	• Treatment-emergent adverse events, change

Objective(s)	Endpoint(s)
relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks; • To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids.	in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.
<u>Pharmacokinetic and Pharmacodynamic</u>	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.
<u>Exploratory</u>	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures (EQ-5D-5L).	• Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3, randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal ultrasound (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during 1 cycle during the screening period. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. Another transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24, followed by a repeat endometrial biopsy. Patients will have paired baseline and end-of-treatment endometrial biopsies, independent of ultrasound results. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken on the immediate day prior to the Week 24 visit.

Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits are provided in Figure 4-2.

Figure 4-1 MVT-601-3001 Study Schematic

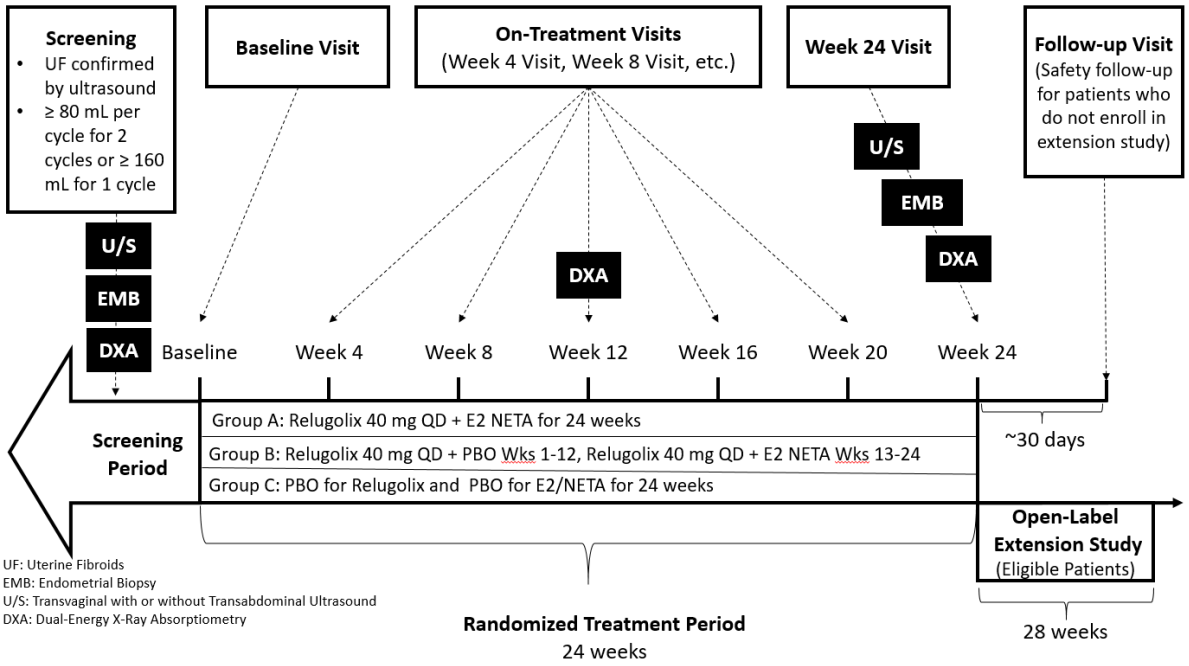


Figure 4-2 Schematic of MVT-601-3001 Screening Visit Scenarios

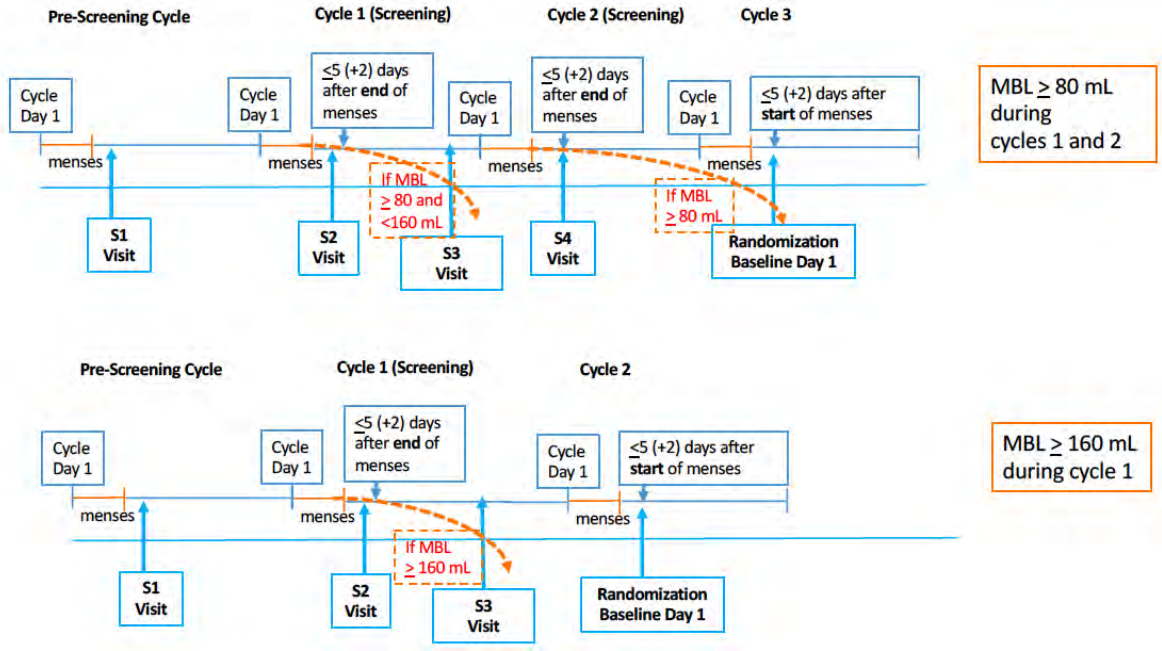


Figure 4-2

Screening visit 1 may be conducted at any time during the pre-screening cycle.

Top scenario:

- Eligibility is based on 2 consecutive screening cycles, each with ≥ 80 mL of menstrual blood loss assessed by the alkaline hematin method where the first screening cycle menstrual blood loss is also < 160 mL.

Bottom scenario:

- Eligibility is based on first screening cycle with ≥ 160 mL menstrual blood loss assessed by the alkaline hematin method.

Additional Scenarios (not depicted):

- Patients whose first screening cycle menstrual blood loss is < 80 mL and whose second screening menstrual blood loss is ≥ 80 mL but < 160 mL may collect menstrual blood loss during a third screening cycle if the first collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is ≥ 80 mL but < 160 mL and whose second screening menstrual blood loss is < 80 mL may collect menstrual blood loss during a third screening cycle if the second collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is < 80 mL may collect menstrual blood loss during a second cycle if the first collection was believed to be inadequate in a highly motivated patient. If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule, and the patient does not need to collect menstrual blood loss for another cycle.

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This study will focus on the primary objective of demonstrating a reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study is designed to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An extension study is planned to provide additional safety and efficacy data through 48 weeks.

Women with uterine fibroids and heavy menstrual blood loss by the alkaline hematin method of ≥ 80 mL/cycle for two cycles or ≥ 160 mL in one cycle during screening will be enrolled in this study. Randomization will be 1:1:1. Placebo was selected as the appropriate control for the study because there is no standard of care medical therapy for the long-term treatment of women with uterine fibroids and heavy menstrual bleeding. Commonly-used treatment options range from combined oral contraceptive pills, which are not effective in many cases, levonorgestrel-containing intrauterine devices, and leuprolide therapy indicated for 3 months in the preoperative setting.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. This dose was selected for evaluation in phase 2 clinical studies based upon phase 1 data demonstrating similar estradiol and progesterone suppression in women treated with single doses of relugolix 40 mg or 80 mg, and data demonstrating that premenopausal women treated with multiple doses of 40 mg once daily relugolix over 14 days had estradiol levels suppressed to a median value of 3.68 pg/mL.

Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, as described above, a phase 2 study of doses of relugolix 10, 20 and 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not

provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 48 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 48 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 1992; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the US as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate has demonstrated that this dose of add-back therapy maintains serum estradiol in the 25-50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy and is not included as a control arm as it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in a well-designed

large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study will primarily assess the efficacy and safety of relugolix 40 mg co-administered with a low-dose of estradiol and norethindrone acetate compared with placebo at 24 weeks to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes. An additional arm with monotherapy relugolix administered for 12 weeks followed by 12 weeks of relugolix co-administered with low-dose hormonal add-back therapy is included to provide data on the requirement for hormonal therapy to mitigate the adverse relugolix side effects of bone mineral density loss and hot flushes.

All eligible women who complete the 24-week study will be offered the opportunity to enroll in an open-label extension study to obtain long-term safety and efficacy data over an additional 28 weeks of treatment, providing approximately 1 year of safety data on the women originally randomized to relugolix.

4.3. Selection of Study Population

The study population will include approximately 390 premenopausal women aged 18 to 50 years with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for randomization and enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Baseline Day 1 visit, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;

4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

    Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

    Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone.
5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use contraception during the study and for 30 days following the last dose of study drug. Specifically agrees to use non-hormonal contraception, as described in Section 4.7 consistently during the Screening period and the Randomized Treatment Period and either nonhormonal or oral contraceptives after return of menses following treatment discontinuation. However, the patient is not required to use specified non-hormonal contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of “post-Essure syndrome” in the investigator’s opinion);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described in Section 4.7;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or < 2 cm are eligible;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;

10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
    d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);
    e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the Screening visit or Baseline Day 1 ECG;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on 2 repeat measures at least 15 minutes apart at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
    d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis,

psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;

17. Is currently pregnant or lactating, or intends to become pregnant during the study period through 1 month after the last dose of study drug or intends to donate ova during the study period or within 2 months after the last dose of study drug;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor;
24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

4.5. Method of Assigning Patients to Treatment Group and Patient ID Number

After a patient is screened, the investigator determines that the patient is eligible for enrollment, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Web Response System (IWRS) during the patient's Baseline Day 1 visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IWRS will also assign the Patient Identification Number (Randomization Number).

4.6. Removal of Patients from Therapy

Completion of the Week 24 defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements. This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; missing multiple study visits; and persistent (> 2 consecutive months) with < 50% of the required number of days of eDiary completion;
- Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain

contact with the patient. The site should attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug, unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of contraception for those for whom one of the above methods do not apply are:

- Condom (male or female condom) with or without spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 2 months following the last dose of study drug.

A patient may start hormonal contraception 4 weeks after her last study dose of study drug provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including just prior to receiving first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

Each patient will be instructed to take one tablet and one capsule per day. The last dose of study drug will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, and color. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

Table 5-1 Description of MVT-601-3001 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An Swedish orange, over-encapsulated round film-coated white tablet with placebo back-fill material	A Swedish orange capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients.

Placebo to match relugolix is a pink tablet using common excipients.

The fixed-dose combination tablet of estradiol 1.0 mg and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3001 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with estradiol / 0.5 mg norethindrone acetate placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule for 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss measured by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state (other than water, tea, or coffee) in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

On selected clinic days, study drug will be administered in the clinic (refer to Sections 1.1 and Section 6.3) or the visits during which patients take study drug in the clinic rather than at home)

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 25°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix, the estradiol/norethindrone acetate combination, relugolix placebo, and the estradiol/norethindrone acetate placebo to be distributed will meet all applicable requirements of the US FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Relugolix 40 mg and relugolix placebo will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate or estradiol/norethindrone acetate placebo.

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding by the investigator for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. The decision to unblind a patient's treatment assignment in an emergency situation resides with the investigator who has direct access to unblind a patient's individual study treatment; however, the investigator should attempt to contact the medical monitor or appropriate study personnel to discuss options before unblinding the patient's treatment assignment unless the urgency of the medical situation precludes this. If unblinding by the investigator occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient. Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment.

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused and used study drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment it may be appropriate to withdraw the patient from the study (see Section 4.6). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zolendronic acid	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone **Note**: All other anticonvulsants are allowed	1 month
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	2 months (6 months for depot subcutaneous or intramusclar injections)
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	2 months (6 months for depot subcutaneous or intramusclar injections)
Hormonal Contraceptives, contraceptive patches and vaginal rings	combined or progestin only Nuva Ring	1 month for patients reporting a typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	1 week

Drug Class	Examples	Window/Comments
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	No prior use if used for reduced bone mineral density Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin clopidogrel tranexamic acid vitamin k preparations factor Xa inhibitors	1 month
Glucocorticoids	prednisolone or prednisone dexamethasone	No window Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration ($\leq$ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir	2 weeks Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Drug Class	Examples	Window/Comments
Moderate and Strong P-glycoprotein Inhibitors	amiodarone atazanavir[f] azithromycin[a] captopril[b] carvedilol[g] clarithromycin[a] cobicistat[f] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	2 weeks (6 months for amiodarone) Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone

a. Roxithromycin is allowed
b. All other angiotensin converting enzyme inhibitors are allowed
c. Tacrolimus is allowed
d. Amlodipine and nifedipine are allowed
e. Fluconazole is allowed
f. Integrase inhibitors are allowed
g. Metoprolol and atenolol are permitted

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

From the Screening 1 visit to the Week 24 (or Early Termination) visit, the recommended analgesics for uterine-fibroid associated pain are as follows:

- First-line: ibuprofen
- Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
- Third-line: opioid or opioid-acetaminophen combination
- Fourth-line: investigator discretion

The purpose of these recommendations is to standardize, to the extent possible, analgesic medication use to facilitate the effects on the secondary endpoint regarding of uterine-fibroid-related pain.

Patients should be instructed not to use analgesics for prophylactic purposes.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL and ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.8. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities in the study synopsis (see Section 1.1). The study is divided into three periods: screening period, randomized treatment period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study; unscheduled visits may also occur as needed to evaluate patients).

6.2. Screening Period

Patients should have a diagnosis of uterine fibroids and a history of heavy menstrual bleeding with or without associated pain on a background of generally regular menses (ie, regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next menstrual period) as reported by the patient for at least 3 months prior to the Screening 1 visit.

The screening period consists of the Screening 1, 2, 3, and 4 visits.

See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening. The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.

6.2.1. Screening 1 Visit

The Screening 1 visit will be conducted following the signing of the informed consent form and may occur at any time during the menstrual cycle. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications, study procedure-related adverse events and any serious adverse events. In addition, vital signs, height, weight, temperature, a complete physical examination, visual acuity assessment, gynecology examination, ultrasound, endometrial biopsy, Papanicolaou test (if needed), clinical laboratory tests, urinalysis, and a urine pregnancy test will be done. Feminine products will be dispensed with instructions to collect and return all products used during the next menses. The paper diary will also be dispensed at this visit and should be completed daily starting with this visit. The bone mineral density scan and mammogram should be scheduled at this time (or within a few days of this visit). Bone densitometry should be scheduled to be prior to the Screening 3 visit and as early as feasible to ensure results are available prior to randomization.

The order of procedures should be as follows. Patients not meeting eligibility criteria after any procedure should not undergo subsequent procedures.

- Medical history and review of prior uterine imaging studies
- Review of concomitant medications (including supplements and over the counter medications)
- Review of inclusion and exclusion criteria
- Urine pregnancy test
- Vital signs, weight, and height
- Complete physical examination and visual acuity assessment
- Ultrasound – do not proceed with additional procedures if no uterine fibroids are identified with the local/initial reading
- Gynecology examination, Papanicolaou test (if need), endometrial biopsy, clinical laboratory tests, including TSH, urinalysis
- Dispense feminine products and paper diary with instructions to begin recording starting information daily, starting on the Screening 1 visit day
- Schedule mammogram (if needed)
- Schedule bone densitometry

The ultrasound will be a transvaginal ultrasound with or without a transabdominal ultrasound (see Section 4.3 ultrasound entry criteria), performed to assess for uterine fibroids. Saline or gel contrast may be used but is not required (see Section 4.3 ultrasound entry criteria). The anatomic location and size of the fibroid disease will be estimated by the local reader. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to

randomization). The investigator, rather than the central reader, will determine if any exclusionary pathology is present. If ultrasound fails to demonstrate fibroids on the local reading, do not proceed with additional Screening visit 1 procedures.

The Papanicolaou test must be conducted for women without a test result within 2 years prior to the Screening 1 visit and the specimen is to be submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

The endometrial biopsy will be obtained with an endometrial suction curette (eg, Pipelle®) and submitted to the Central Laboratory.

The mammogram must be done in patients ≥ 39 years of age by the time of the (anticipated) Baseline Day 1 visit if there is no record (and reading) from within 6 months prior to the screening period.

If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab. Please see Section 5.10.2.2 for guidance on iron therapy.

6.2.2. Screening 2 Visit

Screening 2 visit is scheduled to occur within 5 (+2) days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine products. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine products will be dispensed for collection of menstrual blood loss during the next menses. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab. Women whose laboratory testing reveals iron-deficiency anemia as defined in the study must be started on iron therapy.

Confirm the scheduling of the bone densitometry and mammogram (if needed) and review mammogram results, if available. The mammogram must be normal (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) in order for the patient to be eligible.

Once the menstrual blood loss results from the first cycle are available, schedule Screening 3 visit as soon as feasible and within 5 (+2) days of receiving results showing that the menstrual blood loss is ≥ 80 mL

Patients will be dispensed feminine products to be gathered for the second cycle.

6.2.3. Screening 3 Visit

The patient will return for the Screening 3 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL and within ≤ 15 days after the Screening 2 visit. At the Screening 3 visit, review of inclusion and exclusion criteria will be conducted to confirm continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. At this visit, review the endometrial biopsy results and review mammogram results, if available.

Confirm that the bone densitometry scans have been submitted for central reading. The mammogram and central bone densitometry results must be available prior to randomization.

6.2.4. Screening 4 Visit

The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle. If not skipped, then the Screening 4 visit is scheduled to occur within 5 (+2) days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn for hemoglobin assessment. The patient's eDiary data collection will be reviewed. Laboratory and imaging evaluations will be reviewed to ensure eligibility for randomization.

6.2.5. Menstrual Blood Loss Repeat Collection

At the discretion of the investigator, the collection of menstrual blood loss can be repeated once during the screening period (either after the first or second screening cycle) if one menstrual cycle does not meet the heavy menstrual bleeding alkaline hematin criteria and it is thought to be due to an inadequate collection by a highly motivated patient.

6.2.6. Re-Screening

Patients who fail screening may be re-screened with approval of the medical monitor. Patients undergoing re-screening will sign a new informed consent form and issued a new screening number. For patients who begin re-screening within 10 weeks of signing the original informed consent form, transvaginal ultrasound, endometrial biopsy, and bone densitometry do not need to be repeated, if performed previously.

6.2.7. Retesting

Screening laboratory tests may be repeated once during the Screening period, if necessary, at the investigator's discretion. For laboratory-based entry criteria, the most recent value will be used to determine eligibility. Additional laboratory retesting requires the approval of the medical monitor. Retesting of other procedures (except once, as required, due to technical or logistical issues such as an inadequate sample) also require approval of the medical monitor.

6.3. Randomized Treatment Period (Baseline to Week 24)

At the Baseline Day 1 visit, patients will be randomized to one of the three study treatment arms (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the Week 24 visit. Patients will continue recording daily in their eDiary. On-treatment study visits will occur every 4 weeks through the end of Week 24. At each post-baseline visit, patients will return their feminine products for alkaline hematin testing. Safety monitoring including signs and symptoms directed physical examination, waist circumference, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12

and Week 24 visits. A repeat transvaginal ultrasound (with or without a transabdominal ultrasound) and endometrial biopsy will be performed at the Week 24 visit. The endometrial biopsy will be read centrally. Study drug and eDiary compliance will be reviewed at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the randomized treatment period.

Sites should try to schedule patient visits during the morning, instructing patients to arrive before taking their study drug to allow for pre-dose PK/pharmacodynamic sampling on visits at which these specimens are drawn. Patients must come to the clinic in the fasted state (eg, nothing to eat or drink other than water after midnight the day before the clinic visit) for the Baseline Day 1 and Week 24/Early Termination visits.

For visits *other than* Baseline Day 1 and Week 24/Early Termination, if the clinic visit cannot be scheduled for the morning, patients may eat in the morning but should not have eaten or had anything to drink other than water, coffee, or tea for at least 2 hours prior to the clinic visit and must not eat or drink (other than water, coffee or tea) for at least 1 hour after the clinic visit. In these situations, the laboratory requisitions must indicate that the patient was not fasted for their chemistry and lipid testing.

6.4. Continuation into Extension Study

It is expected that most patients will enter the 28-week extension study (MVT-601-3003), which will be conducted under a separate protocol. Patients will provide separate informed consent to participate in the extension study during which all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate.

6.5. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 24 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 24; however, for patients whose last dose of study drug is during Week 6 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound), endometrial biopsy, and bone densitometry. These procedures may be performed, however, at the investigator's discretion, if they aid in follow-up of ongoing adverse events.

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3003), will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation. Patients who withdraw early from this study will also undergo the Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Refer to the Schedule of Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Additional Safety Follow-Up Procedures

For patients not continuing into the extension study (MVT-601-3003), additional safety procedures are required in some circumstances as described below. These procedures will be performed during unscheduled visits.

- Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.
- Patients with endometrial biopsy findings of endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory. In addition, patients with endometrial hyperplasia with atypia will be evaluated and managed, as needed, by a gynecologist.
- Patients who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.

6.7. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, PK and pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.8. Study Procedures

6.8.1. Efficacy-Related Procedures

6.8.1.1. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.8.1.2. Transvaginal and Transabdominal Ultrasound

Transvaginal with or without transabdominal ultrasound with or without saline or gel contrast is performed for the diagnosis of uterine fibroids, to determine uterine and myoma volumes, and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Transvaginal ultrasound will be performed. Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = $D1 \times D2 \times D3 \times \pi / 6$
Where:
D1 = the longest diameter of the myoma or uterus (unit of length: cm)
D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection “Z”) and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone or when endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.). If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24.

6.8.1.3. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.8.1.4). To maintain blinding, concentrations of these hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.8.1.4. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping procedures are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.8.1.5. Patient Diary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. Patients will complete daily eDiaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will be reviewed by the study staff.

Patients will also receive a paper diary to enter information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit.

6.8.1.6. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 3). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the randomized treatment period. With exception of Baseline Day 1 (see Section 1.1), patients will complete the MIQ at each visit at the site before other study procedures.

6.8.1.7. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL) score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). Patients will complete the UFS-QOL questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit. With the exception of Baseline Day 1 (see Section 1.1), patients will complete the UFS-QOL before other study procedures.

6.8.1.8. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale (EQ-5D-5L) is a standardized instrument for use as a measure of health outcomes (see Appendix 5). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 5-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D-5L questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit. With the exception of Baseline Day 1 (see Section 1.1), patients will complete EQ-5D-5L before other study procedures.

6.8.1.9. Patient Global Assessment for Symptoms and Patient Global Assessment for Function

These simple questions are used by the patient to qualitatively describe severity of symptoms or effects on function (PGA) (see Appendix 6) on a schedule described in the Schedule of Activities (see Section 1.1). With the exception of Baseline Day 1 (see Section 1.1), patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Section 1.1). With the exception of Baseline Day 1, patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site.

6.8.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF.

Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.

6.8.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one sample of blood will be collected and stored for future pharmacogenomic analyses, unless precluded by local law or regulations. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.8.2. Safety-Related Procedures

6.8.2.1. Weight, Height, Waist Circumference, and Body Mass Index

Patients should have weight and height measured while wearing indoor clothing and with shoes removed. Waist circumference should be measured with a measuring tape wrapped around the narrowest portion of the patient’s mid-section.

6.8.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.8.2.3. Physical and Gynecologic Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for women without an available test result from within 2 years prior to the Screening 1 visit and submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

6.8.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory. The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Hemoglobin A1c Creatine Kinase Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase	White Blood Cell (WBC) Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and Clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine Microscopy
	Lipids	**Pregnancy**
	Total Cholesterol Low Density Lipoprotein High Density Lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)
Hormones	**Serology**	**Iron Studies**
Thyroid-Stimulating Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Vitamin D [25(OH)D]	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody	Iron Ferritin

A separate sample will be collected at the Day 1 visit in all patients and will be banked for hepatitis serology (Table 6-1). The samples will be analyzed, if requested, by the medical monitor for evaluation of abnormal liver tests during the study.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, serology, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally. If the hemoglobin is $\leq$ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges for the laboratory or laboratories used.

6.8.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.8.2.6. Endometrial Biopsy

An endometrial biopsy will be obtained using an endometrial suction curette (eg, Pipelle®) and submitted to the central laboratory for reading. If the biopsy is inadequate for diagnosis at either Screening or at Week 24, it should be repeated and sample submitted to the central laboratory. If the second specimen is also inadequate for diagnosis at Screening, the patient is not eligible for the study. Bone Mineral Density

6.8.2.7. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient). The scans will be read by the central radiology laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual patient will be monitored by a central radiology laboratory over the course of the study. Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the anatomical sites assessed during the study. In this case, it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for DXA scanning will be provided in the Study Reference Manual.

Please see Section 6.6 for follow-up of patients who are not continuing into the extension study (MVT-601-3003) and whose bone mineral density has decreased by > 2% at the lumbar spine (L1-L4) or total hip at the Week 24/Early Termination visit relative to Baseline.

6.8.2.8. Visual Acuity

Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see Study Reference Manual for additional details).

Patients whose presenting visual acuity score is 90 or lower at the Baseline visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history.

Patients whose presenting visual acuity score at Week 24 /Early termination has decreased by 10 or more points from Baseline should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

6.8.3. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of blood collected for pharmacogenomics testing (see Section 6.8.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), ECGs, bone mineral density assessments, endometrial biopsy results, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;

- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).
- Events of heavy menstrual bleeding, as heavy menstrual bleeding is being quantitatively measured as an efficacy endpoint, unless the event meets seriousness criteria.

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are 'intermittent'. All other events are 'continuous'. Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events which jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local Institutional Review Board (IRB) or Institutional Ethics Committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's eDiary entries and answers to the UFS-QOL will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Study procedure-related adverse events will be collected from the signing of the informed consent form.

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit approximately 30 days after the last dose of study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

With the exception of adverse events that are considered related to study screening procedures, (which are to be recorded as adverse events), events occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).

- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST $\geq$ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized treatment period or the Follow-up visit should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet SAE criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 7.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the International Normalized Ratio (INR) > 1.5; or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
   - Alcoholic hepatitis
   - Nonalcoholic steatohepatitis
   - Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a Safety Reporting Form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Serious Adverse Event report form and is as follows:

Send completed Safety Report Forms to QuintilesIMS:

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
All Regions	PPD	PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest (AECI) reporting, please call:

- North/South America: PPD
- Regional toll-free phone and fax lines distributed separately. Please refer to Study Reference Manual.

The initial report should include:

- Study number (MVT-601-3001)
- Site address and number
- Investigator name
- Patient ID number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity)
- Causal relationship to the study drug

If the patient died, the report should include the cause of death as the event term (with death as outcome) and whether or not the event leading to death was related to study drug treatment, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the

initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (ie, more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy reporting forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.8.2 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, electrocardiograms and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine fibroids. Low-dose hormonal add-back therapy with estradiol and norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (QTc prolongation), hepatic enzyme increases, PLD, reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density.	Bone mineral density will be monitored at the Baseline Day 1, Week 12, and End of Treatment visits and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-gp inhibitors/inducers.	Collection of adverse events.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec.	12-lead ECG at Baseline Day 1, Week 12 and End of Treatment visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzyme Increase Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal LFTs are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal LFTs (AST or ALT > 3 x ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be checked at the beginning and end of the study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior	Clinical chemistries assessing LFTs, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	hypersensitivity, migraine with aura, porphyria, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% across primary and secondary endpoint testing will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL.

Statistical analyses for all efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the ITT Population who have no relevant major protocol violations, defined as a subset of all major protocol violations (details will be provided in the statistical analysis plan). The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population.

This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at

significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;
- Proportion of women who achieve amenorrhea over the last 35 days of treatment;
- Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24;
- Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain;
- Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11;
- Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20;
- Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29;
- Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity;
- Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life;
- Change in PGA for uterine fibroid related function from Baseline to Week 24;
- Change in PGA for uterine fibroid symptoms from Baseline to Week 24;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities;
- Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;
- Change from Baseline to Week 24 in uterine volume; and

- Change from Baseline to Week 24 in uterine fibroid volume.

The analysis methods used for the primary endpoint will be applied to the analyses of the secondary endpoints of proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment compared between relugolix Group B and placebo Group C, the proportion of patients with amenorrhea over the last 35 days, the proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of at least 1 g/dL at Week 24 and the proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions and stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, UFS-QOL score, PGA for function and symptoms, MIQ Score, Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline. The between treatment comparisons will be performed using model derived least squares means with treatment, stratification factors, baseline result accounted for in the model.

Baseline Numerical Rating Scale score is defined as the average Numerical Rating Scale score from the 35 days of data collected prior to the date of first dose of study drug after randomization. The Numerical Rating Scale score during the final study month is the average Numerical Rating Scale score during the last 35 days on treatment.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment group as treated. The treatment emergent period will be defined as the period of time from the first dose date of the randomized study drug treatment through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, or the date and time of the first dose of open-label extension (MVT-601-3003) study drug, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ

class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each parameter.

ECGs will be read centrally. The distributions of corrected QT interval will be summarized at each visit. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

Bone mineral density will be determined by the central radiology laboratory at the femoral neck, lumbar spine (L1-L4), and total hip. Values at Baseline, Week 12, and Week 24 visits will be summarized by treatment group along with the absolute and percent changes from Baseline and associated 95% confidence intervals. The number and percentage of patients meeting a bone mineral density decline of at least 7% by body area (lumbar, total hip, and femoral neck) will be presented with 95% confidence intervals by treatment group.

To support the inclusion of add-back therapy in the treatment regimen, the safety endpoint of mean percent change from Baseline in bone mineral density lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal comparison of Group A versus Group B (see details in the joint statistical analysis plan).

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by treatment arm.

9.5. Pharmacokinetic and Pharmacodynamic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoint. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoint will be assessed:

- Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Council on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed

consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the IB, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the IB, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
    - Patient identification (name, date of birth, gender);
    - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
    - Participation in the study (including study number);
    - Study discussed and date of informed consent;
    - Dates of all visits;
    - Documentation that protocol-specific procedures were performed;
    - Results of efficacy parameters, as required by the protocol;
    - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
    - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
    - Concomitant medication (including start and end date); and
    - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory

authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 90 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 120 days in order to obtain patent protection if deemed necessary.

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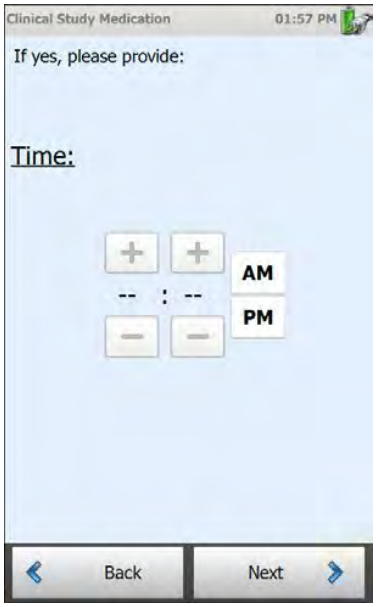
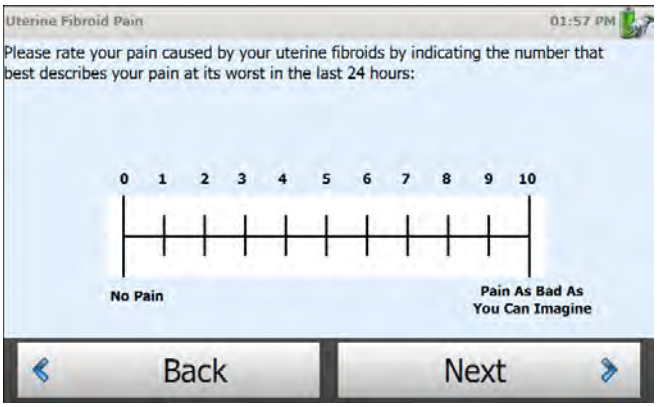
APPENDICES

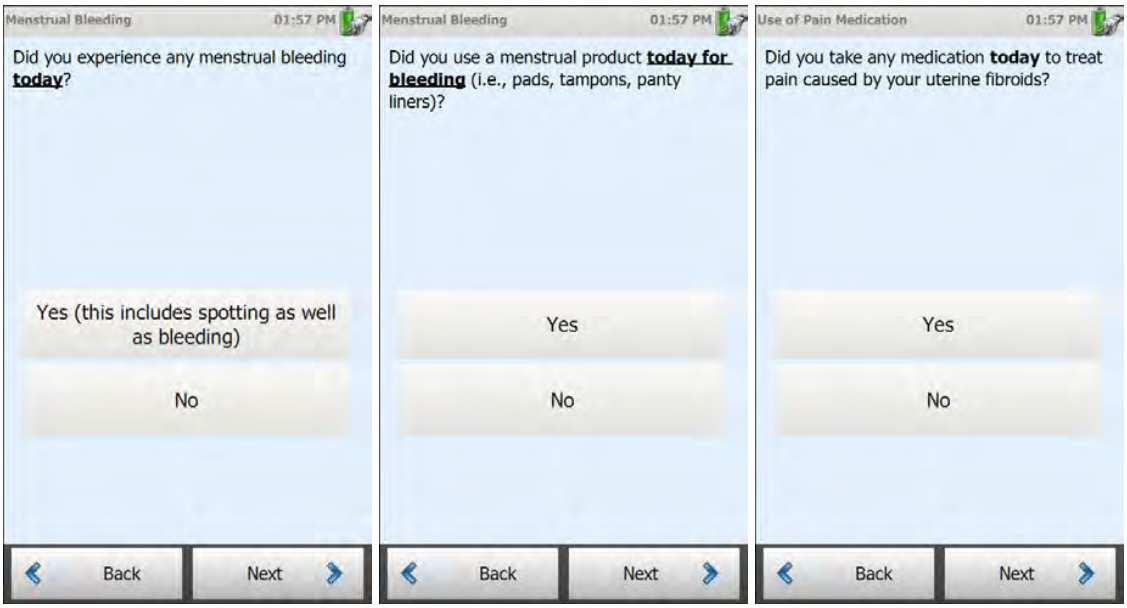
Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

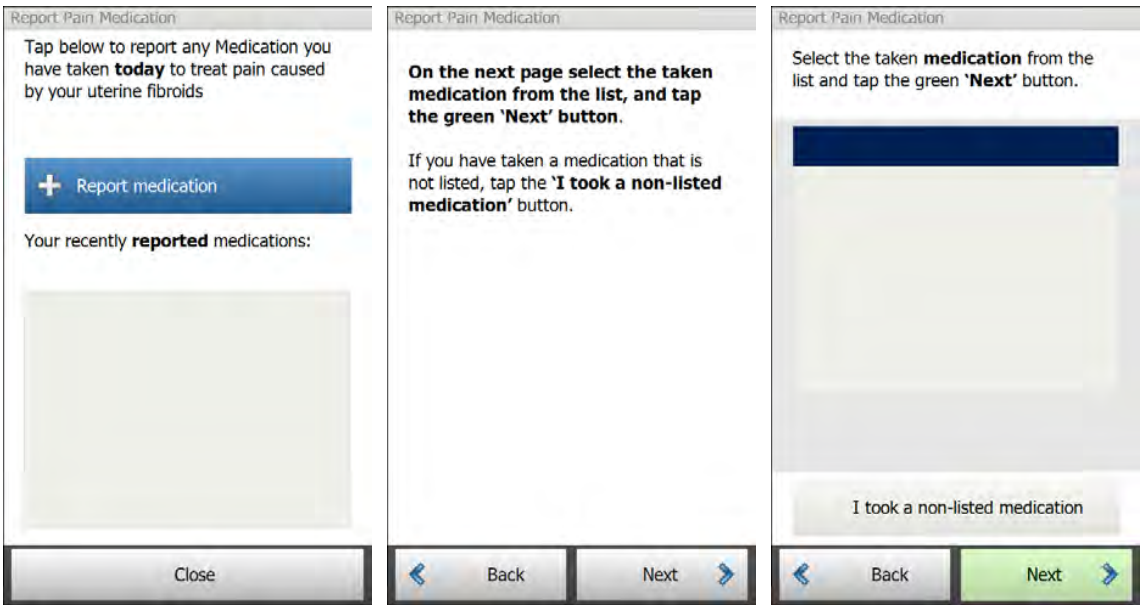
Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

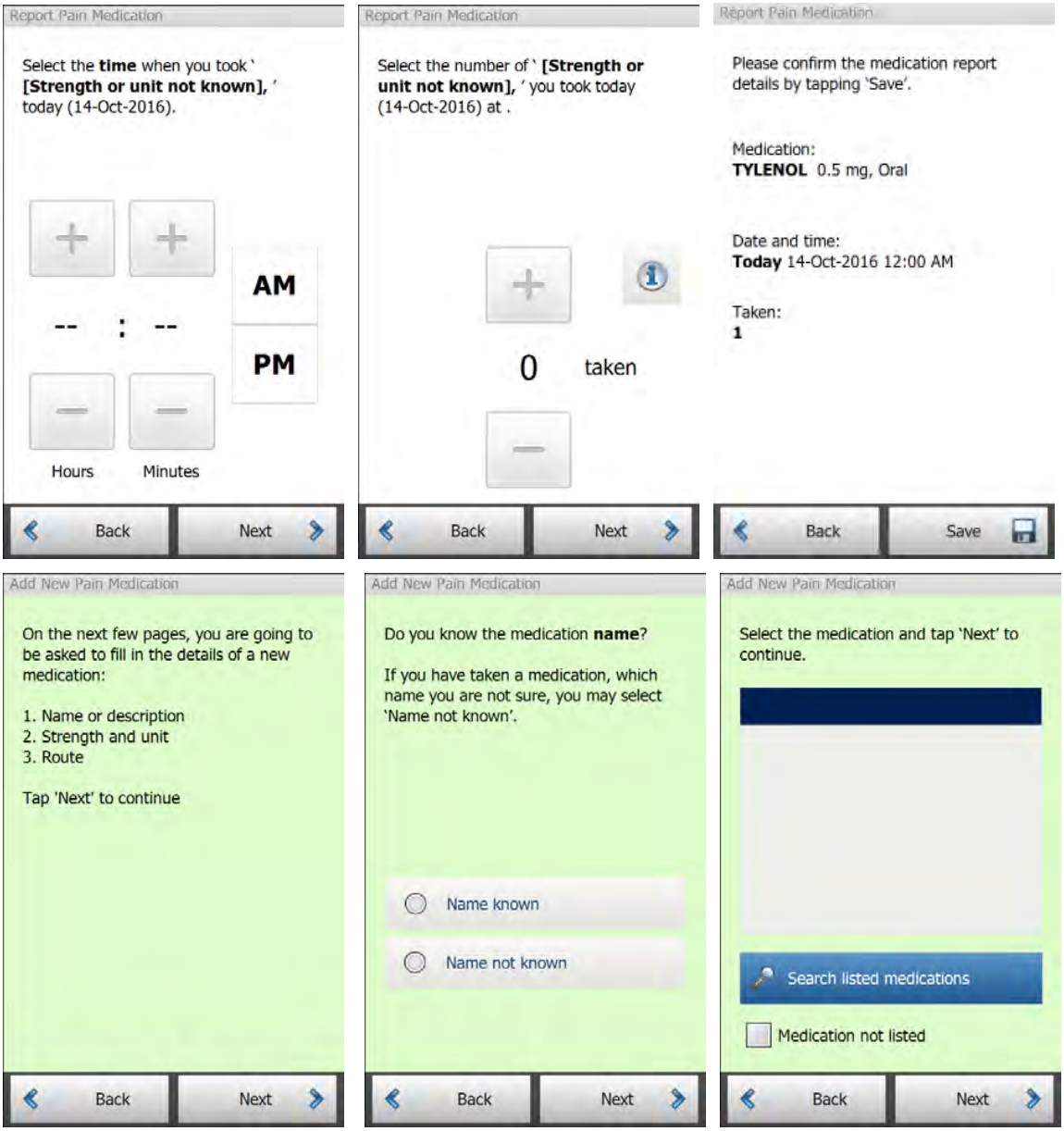
Appendix 2. Daily eDiary

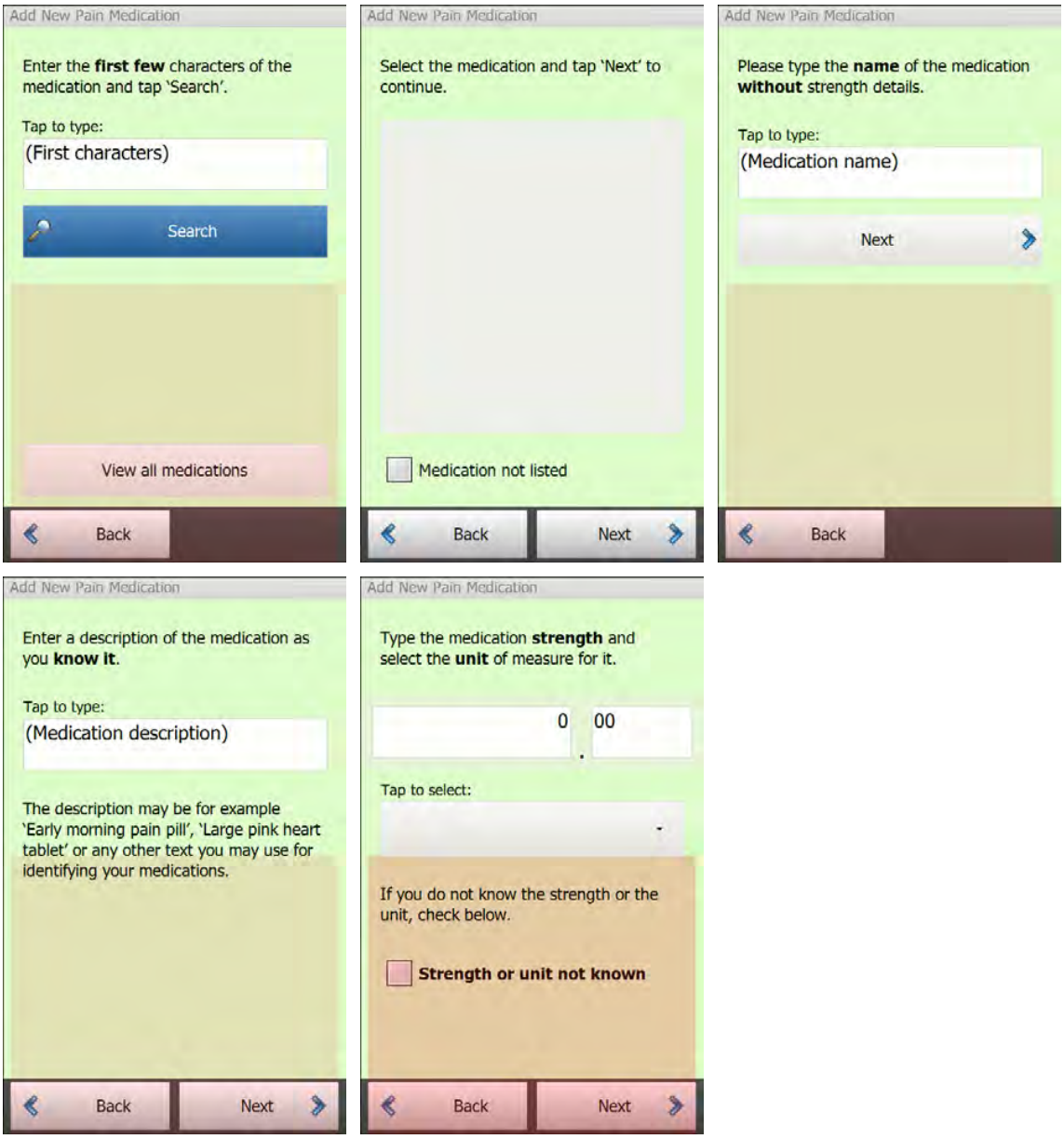


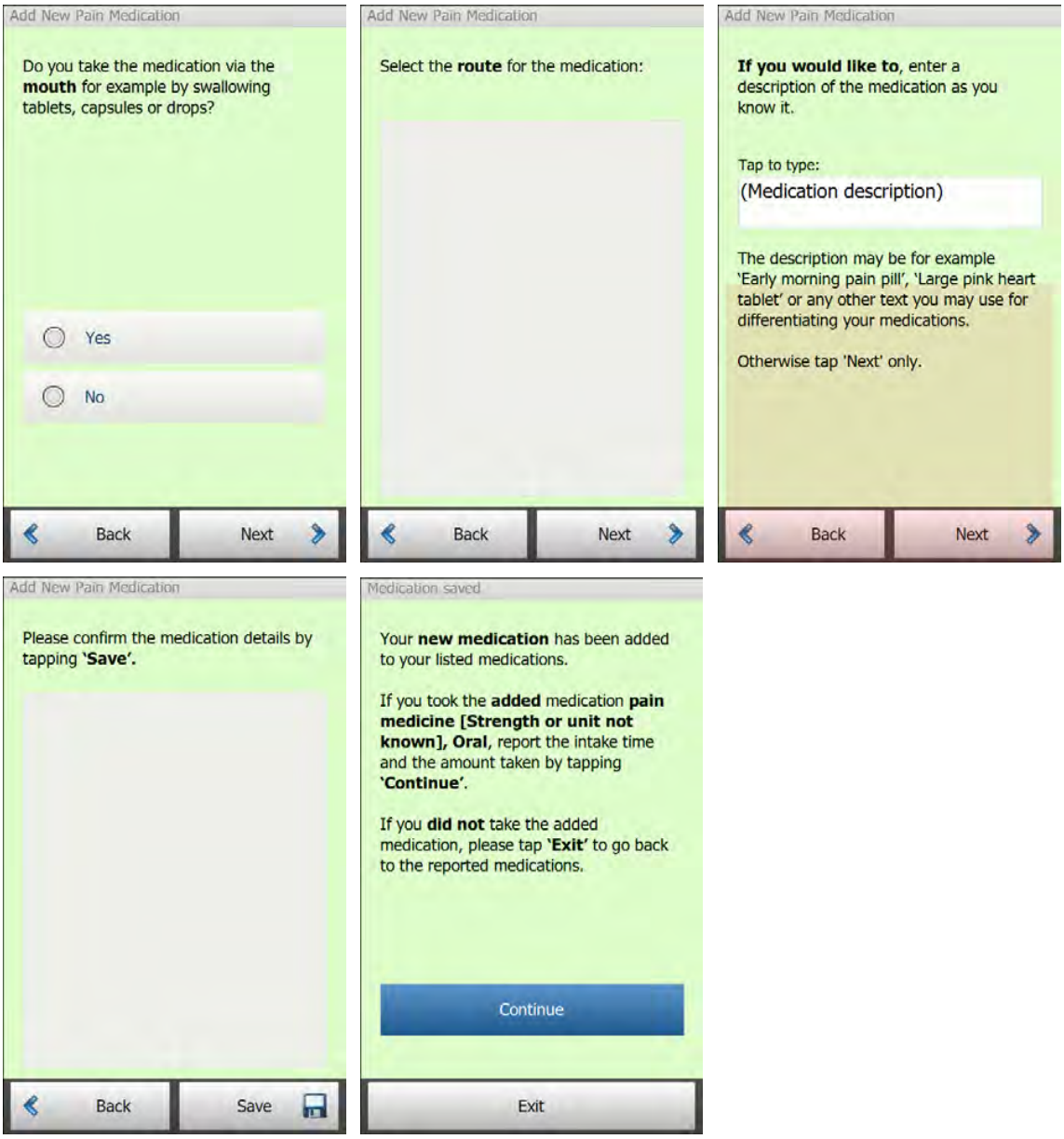



Menstrual Bleeding
01:57 PM
Did you experience any menstrual bleeding **today**?
Yes (this includes spotting as well as bleeding)
No
Back
Next
Menstrual Bleeding
01:57 PM
Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?
Yes
No
Back
Next
Use of Pain Medication
01:57 PM
Did you take any medication **today** to treat pain caused by your uterine fibroids?
Yes
No
Back
Next


Report Pain Medication
Tap below to report any Medication you have taken **today** to treat pain caused by your uterine fibroids
Report medication
Your recently **reported** medications:
Close
Report Pain Medication
On the next page select the taken medication from the list, and tap the green 'Next' button.
If you have taken a medication that is not listed, tap the **'I took a non-listed medication'** button.
Back
Next
Report Pain Medication
Select the taken **medication** from the list and tap the green **'Next'** button.
I took a non-listed medication
Back
Next


Report Pain Medication
Select the **time** when you took ' **[Strength or unit not known],** ' today (14-Oct-2016).
AM
PM
-- : --
Hours
Minutes
Back
Next
Report Pain Medication
Select the number of ' **[Strength or unit not known],** ' you took today (14-Oct-2016) at .
0 taken
Back
Next
Report Pain Medication
Please confirm the medication report details by tapping 'Save'.
Medication:
TYLENOL 0.5 mg, Oral
Date and time:
Today 14-Oct-2016 12:00 AM
Taken:
1
Back
Save
Add New Pain Medication
On the next few pages, you are going to be asked to fill in the details of a new medication:
1. Name or description
2. Strength and unit
3. Route
Tap 'Next' to continue
Back
Next
Add New Pain Medication
Do you know the medication **name**?
If you have taken a medication, which name you are not sure, you may select 'Name not known'.
Name known
Name not known
Back
Next
Add New Pain Medication
Select the medication and tap 'Next' to continue.
Search listed medications
Medication not listed
Back
Next


Add New Pain Medication
Enter the first few characters of the medication and tap 'Search'.
Tap to type:
(First characters)
Search
View all medications
Back
Add New Pain Medication
Select the medication and tap 'Next' to continue.
Medication not listed
Back
Next
Add New Pain Medication
Please type the name of the medication without strength details.
Tap to type:
(Medication name)
Next
Back
Add New Pain Medication
Enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for identifying your medications.
Back
Next
Add New Pain Medication
Type the medication strength and select the unit of measure for it.
0
00
Tap to select:
If you do not know the strength or the unit, check below.
Strength or unit not known
Back
Next


Add New Pain Medication
Do you take the medication via the **mouth** for example by swallowing tablets, capsules or drops?
Yes
No
Back
Next
Add New Pain Medication
Select the **route** for the medication:
Back
Next
Add New Pain Medication
If you would like to, enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for differentiating your medications.
Otherwise tap 'Next' only.
Back
Next
Add New Pain Medication
Please confirm the medication details by tapping **'Save'.**
Back
Save
Medication saved
Your **new medication** has been added to your listed medications.
If you took the **added** medication **pain medicine [Strength or unit not known], Oral**, report the intake time and the amount taken by tapping **'Continue'**.
If you **did not** take the added medication, please tap **'Exit'** to go back to the reported medications.
Continue
Exit

Appendix 3. Menorrhagia Impact Questionnaire

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

Pt. Initials: _____ **Pt. ID:** _____

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐	☐	☐	☐	☐
2. Passing blood clots during your menstrual period	☐	☐	☐	☐	☐
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐	☐	☐	☐	☐
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐	☐	☐	☐	☐
5. Feeling tightness or pressure in your pelvic area	☐	☐	☐	☐	☐
6. Frequent urination during the daytime hours	☐	☐	☐	☐	☐
7. Frequent nighttime urination	☐	☐	☐	☐	☐
8. Feeling fatigued	☐	☐	☐	☐	☐

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Made you anxious about traveling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Interfered with your physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Caused you to feel tired or worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Made you feel as if you are not in control of your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Made you concerned about soiling underclothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Made you feel less productive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Made you feel self-conscious of weight gain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Made you feel that it was difficult to carry out your usual activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Interfered with your social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Made you feel conscious about the size and appearance of your stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Made you concerned about soiling bed linen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐	☐	☐	☐	☐
24. Made you feel down hearted and blue?	☐	☐	☐	☐	☐
25. Made you feel wiped out?	☐	☐	☐	☐	☐
26. Caused you to be concerned or worried about your health?	☐	☐	☐	☐	☐
27. Caused you to plan activities more carefully?	☐	☐	☐	☐	☐
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐	☐	☐	☐	☐
29. Caused you embarrassment?	☐	☐	☐	☐	☐
30. Made you feel uncertain about your future?	☐	☐	☐	☐	☐
31. Made you feel irritable?	☐	☐	☐	☐	☐
32. Made you concerned about soiling outer clothes?	☐	☐	☐	☐	☐
33. Affected the size of clothing you wear during your periods?	☐	☐	☐	☐	☐
34. Made you feel that you are not in control of your health?	☐	☐	☐	☐	☐
35. Made you feel weak as if energy was drained from your body?	☐	☐	☐	☐	☐
36. Diminished your sexual desire?	☐	☐	☐	☐	☐
37. Caused you to avoid sexual relations?	☐	☐	☐	☐	☐

Appendix 5. European Quality of Life Five-Dimension Five-Level Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

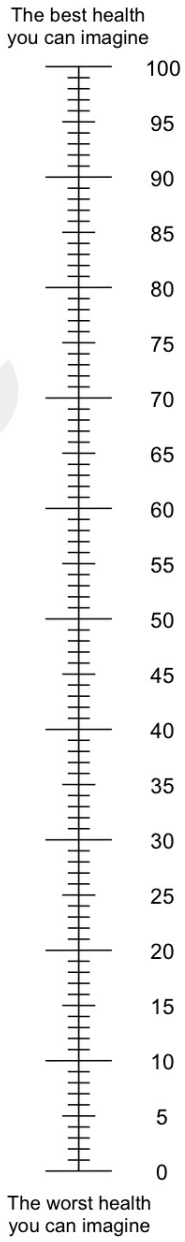
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6. Patient Global Assessments

Patient Global Assessment (for function)

How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. No limitation at all
2. Mild limitation
3. Moderate limitation
4. Quite a bit of limitation
5. Extreme limitation

Patient Global Assessment (for symptoms)

How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. Not severe
2. Mildly severe
3. Moderately severe
4. Very severe
5. Extremely severe

Appendix 7. Assessment of Abnormal Liver Function Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with low-dose estradiol and norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

h. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Appendix Table 1[a]; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • CBC with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.; • Serology for celiac disease; • Appropriate liver imaging; • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 08-FEB-2017

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3001

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

08Feb2017
Date

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AMENDMENT 1: SUMMARY OF CHANGES

Item; Section(s)	Original	Amendment 1	Rationale
Study Title	An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids	To add the study moniker
Sponsor Signature Page		Biostatistics and Medical Director signatories added; CEO signatory removed	To update signatories based on personnel additions
IC #3; Synopsis, 4.1	"Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);"	None	Weight restriction, other than as related to DXA scanner accommodation (covered in EC #4) was not needed.
IC #5 (now IC #4); Synopsis, 4.1, 4.3.1, 6.2, 6.3, SOA footnote q	"Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal ultrasound performed with saline or gel contrast during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria: a. Subserosal, intramural, submucosal non-pedunculated fibroid with a diameter $\geq$ 2 cm (longest diameter), or b. Multiple small fibroids with a total uterine volume of $\geq 130\ cm^3$"	"Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria: a. Subserosal, intramural, or <50% intracavitary submucosal fibroid with a diameter $\geq$ 2 cm (longest diameter), or b. Multiple small fibroids with a total uterine volume of $\geq 130\ cm^3$; Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size. Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with	To clarify situations in which a transabdominal ultrasound and saline or gel infusion should be performed

Item; Section(s)	Original	Amendment 1	Rationale
		transvaginal ultrasound alone."	
EC #5; Synopsis, 4.3.2	Has a baseline bone mineral density z-score < -2.0 at spine or total hip	Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck	To exclude patients with baseline bone mineral density z-score of < -2.0 at femoral neck
Placebo Matching; Synopsis, 5.1	Placebo and active tablets and capsules will matched for size, shape, color, and odor	Placebo and active tablets and capsules will matched for size, shape, and color	Odor is not being specifically tested.
IC #4 (now IC #5); Synopsis, 4.1, 4.2, 4.3, 4.3.1, Figure 4-1, Figure 4-2	"Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period"	"Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL for 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period"	To allow patients who have demonstrated menstrual blood loss that is double or more the screening requirement in a single cycle to enroll based on menstrual blood loss data from only one cycle, rather than two
IC #7 (now IC #6); Synopsis, 4.1, 4.3.1	"…not expected to be a candidate for gynecological surgery or ablation procedures…"	"…not expected to undergo gynecological surgery or ablation procedures for uterine fibroids…"	To clarify the criterion's intent
IC #9 (now IC #8); Synopsis, 4.1, 4.3.1, 4.7	"Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram"	"Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure™ syndrome" in the investigator's opinion)"	To exclude women with the potential confounding factor of post-Essure syndrome
IC #10 (now IC #9); Synopsis, 4.1, 4.3.1	"Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer)"	"Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded."	To remove endometritis as an exclusion and to make polyp exclusion consistent with other entry criteria

Item; Section(s)	Original	Amendment 1	Rationale
IC #11 (now IC #10); Synopsis, SOA footnote p, 4.1, 4.3.1, 6.2.1, 6.2.2	"If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period."	"If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period."	To align with recommended mammography screening intervals, accounting for an ~6-month Treatment Period; Disallow patients with BI-RADS 3 readings due to their higher risk
IC #12; Synopsis, 4.3.1	A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.	None	To define the use of randomization authorization in the study procedural documents rather than in the protocol
EC #1; Synopsis, 4.1, 4.3.2, 6.2, SOA footnote q	"Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment."	"Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥2.0 cm, large simple ovarian cyst >4.0 cm, endometrioma(s) >4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study. Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (e.g., suspected intrauterine masses, equivocal endometrial findings, etc.)."	To add examples of common findings that would be considered exclusionary; To clarify situations in which saline or gel infusion should be performed; To allow patients with finding not requiring immediate evaluation or treatment to enroll

Item; Section(s)	Original	Amendment 1	Rationale
EC #2; Synopsis, 4.3.2	"Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle"	"Has known rapidly enlarging uterine fibroids in the opinion of the investigator"	To remove an exclusion that may be a disease-state manifestation and to add an exclusion for uterine fibroids at higher risk to be malignant
EC #10g, h; Synopsis, 4.3.2	none	"Migraine with aura" "History of porphyria"	To add migraine with aura as an example of a contraindication to treatment with low-dose estradiol and norethindrone acetate and to add an exclusion for porphyria, which is listed in the prescribing information in some countries
EC #12; Synopsis, 4.3.2	"Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study."	"Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative."	To incorporate high-risk human papilloma virus reflexive testing that will be performed by the central laboratory into the criterion

Item; Section(s)	Original	Amendment 1	Rationale
EC #14b, d, h; Synopsis, 4.3.2	"History of angina" "History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute)" "Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram"	"History of angina or significant coronary artery disease (i.e. ≥50% stenosis)" "History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute)" Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness"	To add an exclusion for significant coronary artery disease (#14b), to remove the exclusion for pacemaker (criterion was internally inconsistent) (#14d), and to allow for physiologically appropriate bradycardia in physically-fit patients (#14h)
EC #16c; Synopsis, 4.3.2	"History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year)"	"Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled."	To broaden the ability for patients with remote psychiatric disorders and current psychiatric disorders who are able to participate in the trial to be enrolled
EC #17; Synopsis, 4.3.2	"Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study"	"Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug"	To clarify timing relative to last dose of study drug
Study Completion; 4.6	None	Added definition of study completion (completion of Week 24 visit)	To include a definition

Item; Section(s)	Original	Amendment 1	Rationale
Removal of Patients from Therapy; 4.6, 6.7.2.6	Patients who have percent change from Baseline in bone mineral density at either the Week 12 or Week 24 visit (or any unscheduled visit) at the lumbar spine (average L1-L4), total hip, or femoral neck of < -4.0 that is repeated and confirmed (ie, both values are < -4.0)	Replaced with alert notifications from the central radiology readers to the investigator for a 7% or greater decline in bone mineral density at any time point (added to section 6.7.2.6)	To allow for use of clinical risk assessment by the investigator in determining whether withdrawal is warranted and determination of future management. The study is conducted in patients generally considered at low risk for fracture; Patients with history of osteoporosis, or baseline bone mineral density Z-scores < -2.0 are excluded.
Identification of Investigational Product; 5.0. Table 5-1	No color listed Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™ or Activelle™).	"Swedish orange" added in the description for the placebo and active low-dose add back capsule Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™ or Activelle™).	To add product details
Product Characteristics; Section 5.2.1	Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the United States Pharmacopeia and the National Formulary (USP/NF) excipients.	"Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients. Placebo to match relugolix is a pink tablet using common excipients."	To facilitate review of the protocol in European countries, USP language was made more general

Item; Section(s)	Original	Amendment 1	Rationale
Study Drug Storage; 5.6	"Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 1°C to 30°C until it is used or returned to the sponsor (or designee)."	"Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 25°C with excursion to 15°C to 30°C permitted, until it is used or returned to the sponsor (or designee)."	To narrow the storage temperatures for both relugolix/placebo and estradiol/ norethindrone to match the temperature requirements for Activella
Study Drug Administration; 5.4, 6.3	None	Fasting does not require withholding of water. On clinic visit days that are not in the morning, patients should fast for at least 2 hours prior to the visit and for 1 hour taking the study drug.	To provide clarifications on study procedures
Blinding; 5.7	Investigator to determine if treatment assignment of a site-unblinded patient should be revealed to the sponsor. Sponsor may unblind for a serious adverse event.	Investigator not to reveal treatment assignment of a site-unblinded patient to the sponsor. Sponsor unblinding for serious adverse events described in the Safety Management Plan.	To make this decision a sponsor responsibility; To provide details and context for unblinding of serious adverse events by the Sponsor in the Safety Management Plan, rather than in the protocol
Prohibited Medications; 5.10.1	None	Contact the medical monitor for approval and guidance on study drug administration if a short course of a prohibited P-glycoprotein inhibitor or inducer is required during the study	To provide additional guidance for such situations
Prohibited Medications; 5.10.1	None	Addition of bazedoxifene, zoledronic acid, and factor Xa inhibitors to Table 5-3	To include additional examples of prohibited medications
Prohibited Medications; 5.10.1	Oral contraceptive exclusion period 2 months	Oral contraceptive exclusion period typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months	To shorten exclusionary period for patients following resumption of menses

Item; Section(s)	Original	Amendment 1	Rationale
Prohibited Medications; 5.10.1	Selective progesterone receptor modulator exclusion period 2 months	Selective progesterone receptor modulator exclusion period 6 months	To avoid possible confounding related to the endometrial effects of these drugs
Prohibited Medications; 5.10.1	Bone agent exclusion period 2 months prior to Screening	Bone agent exclusion period indefinite if used for low bone mineral density	To make consistent with eligibility criteria
Prohibited Medications; 5.10.1	None	Addition of 1-week exclusionary window for over the counter and herbal products with known hormonal activity	To reduce possible confounding of efficacy and safety due to these products
Analgesic Medications; 5.10.2.1	Specific required medications for uterine fibroid pain and other pain	Requirements changed to recommendations for allowed medications for uterine fibroid pain. Restriction on analgesics for other pain conditions removed.	To liberalize restrictions based on site feedback while encouraging consistency in analgesic use
Adverse Event Reporting Period; 6.2, 7.2.1, SOA footnote f	Non-serious adverse events occurring after signing of the informed consent form and prior to start of study drug should be recorded as medical history	Non-serious adverse events occurring after signing of the informed consent form and prior to start of study drug should be recorded as adverse events rather than medical history if they are considered related to study procedures; otherwise, they should be recorded as medical history.	To capture study procedure-related adverse events as adverse events
Waist Circumference; SOA, 6.3. 6.7.2.1	None	Waist circumference measured at Baseline Day 1	To obtain data to characterize patients with metabolic syndrome
Ultrasound Procedures; 6.2	None	Addition of clarification that the investigator, rather than the central reader, will determine if any exclusionary pathology is present.	Clarification
Pathology Specimens; SOA footnotes i and r, 6.2, 6.3, 6.7.1.3	Whether the Papanicolaou test and would be locally or centrally read was not specified Endometrial biopsy to be read locally (or centrally read if requested)	Papanicolaou test and endometrial biopsy will be centrally read	To improve consistency of readings and to facilitate site logistics
Unscheduled	None	Reminder add to obtain unscheduled iron studies at Visit 2 if hemoglobin	To improve adherence to the

Item; Section(s)	Original	Amendment 1	Rationale
Iron Studies; 6.2		is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal.	protocol requirements
Pre-Screening Procedures; 6.2	Pre-screening procedures	None	To allow sites to utilize site-specific practices for pre-screening
Re-Screening Procedures; 6.2, SOA	None	Certain screening procedures do not need to be repeated for patients who re-screen within 10 weeks of the signing the original informed consent form: transvaginal ultrasound, endometrial biopsy, and bone densitometry.	To reduce patient procedural burden
Early Termination Procedures; 6.5, SOA footnote s	None	Certain early termination visit procedures are not required for patients whose last dose of study drug is during Week 6 or earlier (transvaginal ultrasound, endometrial biopsy, and bone densitometry). These procedures may be done if they will aid in the evaluation of an ongoing adverse event	To reduce patient procedural burden
Unscheduled Visit Procedures; 6.6, SOA	List of procedures to be done to further evaluate adverse events	Adverse events are to be evaluated and concomitant medications, and reason for visit are to be recorded. Other procedures may be done as needed.	Clarification of required and optional procedures at Unscheduled Visits
Clinical Laboratory Tests; 6.7.2.4, Table 6-1, SOA footnote j	Subset of central laboratory tests	All central laboratory tests	To include full list of clinical laboratory tests and to add Vitamin D at Baseline Day 1
Bone Mineral Density; 6.7.2.6	Incomplete details of bone mineral density acquisition and reporting included in this section.	Details of bone mineral density acquisition and reporting moved to the imaging charter.	To have a single document with the full details of this procedure
Endometrial Biopsy 6.7.1.3	None	Specification that a pipelle should be used for the endometrial biopsy	To have greater uniformity in the specimen acquisition
Pregnancy; 7.2		Requirement for reporting partner pregnancies removed	All study patients will be women

Item; Section(s)	Original	Amendment 1	Rationale
Serious Adverse Event Logistics; 7.6	None	Contact information for serious adverse event reporting added	To update with the serious adverse event vendor's logistical details
Safety Analyses; 9.4	The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5% or 6% by body area (lumbar, total hip, and femoral neck) will be estimated with 95% confidence intervals by treatment group. The number and percentage of patients meeting a T-score of < -2.5 by body area will also be estimated with 95% confidence interval by treatment group.	The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar, total hip, or femoral neck) will be estimated with 95% confidence intervals by treatment group.	To align with the statistical analysis plan and remove references to analyses based on cut-offs for T-scores; analyses based on Z-scores will be detailed in the SAP
Schedule of Papanicolaou Testing; SOA	Screening and Week 24/Early Termination	Screening	Procedure not needed because cervical dysplasia not a safety risk in this trial
Schedule of PD Measurements; SOA	Screening 1 visit, Day 1, Weeks 4, 8, 12, 16, 20, 24, and Follow-up	Day 1, Weeks 4, 12, 24, and Follow-up	To remove unneeded sampling time points
Visit Windows; SOA, Figure 4-2, 6.2	Screening 3 visit: Window $\leq$ 10 days after Screening 2 visit Transvaginal ultrasound, gynecology examination, papanicolaou test, endometrial biopsy, mammogram, bone densitometry: Visit 3 Screening 1, 2, and 4 visits to occur within 4 days of end of menses and Baseline Day 1 visit to occur within 4 days of end of menses	Screening 3 visit: Window $\leq$ 15 days after Screening 2 visit. Transvaginal ultrasound, gynecology examination, papanicolaou test, endometrial biopsy, mammogram (schedule appointment), bone densitometry (schedule appointment): Visit 1 Screening 2 and 4 visits to occur within 5(+2) days of end of menses. Screening visit 1 not timed with menses. Screening 4 visit may be skipped if menstrual blood loss with the first cycle collection is $\geq$160 mL.	To improve site logistics and to accommodate turnaround time for patients collecting 1 cycle of menstrual blood loss

Item; Section(s)	Original	Amendment 1	Rationale
Schedule of Visual Acuity Testing and eDiary; SOA footnote u and v, 6.2	Visual acuity at Screening and on Day 1 eDiary: dispense at Screening 3 visit	Visual acuity on Day 1 Paper diary: dispense at Screening 1 visit eDiary: dispense at Screening 1 visit	To remove an unneeded procedure; visual acuity is not an eligibility criterion; therefore, not needed at Screening To allow fuller data capture of menses dates and daily feminine product use
eDiary; Appendix 2	eDiary question text	eDiary screenshots, which also include analgesic medication dose, route, and frequency questions	To update with final e-diary content
UFS-QoL; Appendix 4			To update with correct version of the instrument
CTCAE and IB version; 2.4.2.2 and various	CTCAE, Version 5.0 IB Version 9.0, dated 09 November 2016	CTCAE version not specified in protocol, but the version to be used will be in the study reference manual and noted in the statistical analysis plan.	CTCAE version 5.0 not yet published at the time of study start; IB version removed to avoid discrepancies that may occur when IB is updated during the study
Minor Edits; Various		Corrections of typos, minor clarifications, minor inconsistencies, and minor wording changes	To improve readability and understandability.

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CEO, Chief Executive Officer; CTCAE, Common Terminology Criteria for Adverse Events, DXA, dual x-ray absorptiometry; EC, exclusion criterion; IB, investigator brochure; IC, inclusion criterion; PD, pharmacodynamic; SOA, schedule of activities; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 08-FEB-2017

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3001

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

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INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
EQ-5D	European Quality of Life Five-Dimension Five-Level
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menstrual Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart

Term	Explanation
PD	pharmacodynamics
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3001
Location	Multinational, including North and South America, Europe, and Australia
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	<u>Primary Efficacy Objective</u> • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. <u>Secondary Efficacy Objectives</u> • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.
	Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.

Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during 1 cycle during the screening period. During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24, followed by a repeat endometrial biopsy. Patients will have paired baseline and end-of-treatment endometrial biopsies, independent of ultrasound results. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine

and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of $\leq$ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
   a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter $\geq$ 2 cm (longest diameter), or
   b. Multiple small fibroids with a total uterine volume of $\geq$ 130 cm^3

      Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

      Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone;
5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of $\geq$ 160 mL during 1 cycle or $\geq$ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in

Section 4.7) consistently during the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:

a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;

9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study.

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate,

including:

a. Known, suspected, or history of breast cancer;
b. Known or suspected estrogen-dependent neoplasia;
c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
g. Migraine with aura;
h. History of porphyria;

11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, $\geq$ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate $\geq$ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening

visit or the Baseline Day 1 visit;

h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;

15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary window periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color.
Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. Primary Efficacy Endpoint • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume. Safety Endpoints • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations ($C\tau$) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.

	Exploratory Endpoints • Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of 260 (130 patients in each of the relugolix and placebo arms) will provide > 99% power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by

MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3001

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)		Within 5 (+2) days after completion of Screening 1 menses	Within ≤ 15 days after Screening 2 visit	Within 5 (+2) days after completion of 2nd Screening menses	Within 7 days of the start of menses	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X[e]	X
Waist circumference					X								
Height	X												
Weight	X				X						X	X[e]	X
Temperature	X				X						X	X[e]	
Adverse Event Collection[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity[h]					X						X	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Complete Physical excluding GYN Examination	X				X						X		
GYN Examination with Pap Test, if applicable	X[i]												
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X[e]	X
12-Lead Electrocardiogram			X		X			X			X	X[e]	X
Clinical Laboratory Tests[j]	X	X			X[k]	X	X	X	X	X	X[l]	X[e]	X
PK Sample[m]					X	X		X			X	X[e]	
PD Sample[n]					X	X		X			X	X[e]	X
Daily Study Drug Administration					X							X[e]	
Administer Dose of Study Drug in Clinic					X	X	X	X	X	X	X	X[e]	
PGx Sample[o]					X							X[e]	
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X	X[e]	
Urinalysis	X				X							X[e]	
Mammogram[p]	schedule	X											
Transvaginal Ultrasound (with or without Transabdominal Ultrasound)[q]	X										X[s]	X[e]	
Endometrial Biopsy[r]	X										X[s]	X[e]	
Bone Densitometry[t]	schedule	X						X			X[s]	X[e]	
Randomization					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X		X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Dispense Study Treatment					X	X	X	X	X	X		X[e]	
Patient paper diary/ eDiary[u]	X	X	X	X	X	X	X	X	X	X	X	X[e]	
Feminine Product Collection and Venous Blood Sample[v]		X		X		X	X	X	X	X	X	X[e]	
MIQ					X	X	X	X	X	X	X	X[e]	
UFS-QoL					X			X			X	X[e]	
EQ-5D					X						X	X[e]	
Treatment Compliance						X	X	X	X	X	X	X[e]	
Status of Menstruation Recovery													X

Notes:
Abbreviations: EQ-5D, European Quality of Life Five-Dimension Five-Level Scale; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; GYN, gynecology; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life
For patients who are re-screening, please see Section 6.2.6 for abbreviated screening procedures.

a. The screening period should be initiated after the informed consent form is signed and any exclusionary windows for prohibited medications has been confirmed.
b. Visit to occur within 5 (+2) days of the completion of menses. Visit 4 should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.
c. Visit to occur within ≤ 15 days after Screening 2 visit; eDiary dispensation must occur at least 7 days prior to Baseline Day 1. The alkaline hematin menstrual blood loss collection may be repeated once at the discretion of the investigator if one menstrual cycle does not meet menstrual blood loss criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose pharmacodynamic sample, pregnancy and urinalysis test samples prior to first dose of study drug. The patient must complete MIQ, UFS-QoL, and EQ-5D questionnaires prior other study procedures and prior to first dose of study drug.
e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
f. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003) and/or terminate early from the study, a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational

agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~4 weeks after an Early Termination visit).

g. Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure) through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first.
h. Visual acuity must be assessed with the study eye chart. The patient should wear any prescription glasses or contacts during the assessment.
i. Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit. The specimen should be submitted to the central laboratory during screening. Another test should be performed for inadequate or false-positive results and be submitted to the central laboratory.
j. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests.
k. At the Baseline Day 1 visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, Vitamin D, iron, ferritin, and hemoglobin A1c. An additional sample will be collected at this visit in all patients and stored for possible future testing for presence of hepatitis A, B, and C if required per request from medical monitor to assess etiology of liver test abnormalities.
l. At the Week 24 visit or Early Termination visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.
m. Pharmacokinetics samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics sample collections are complete.
n. Pharmacodynamic samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Early Termination and Follow Up visits when no dose is administered).
o. Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive)
p. Patients ≥ 39 years of age at the time of the anticipated Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period; if not, schedule at the Screening 1 visit.
q. Transvaginal ultrasound with or without transabdominal ultrasound must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm. Results must be submitted to and uterine fibroid criteria confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is required. See inclusion criterion #5 and exclusion criterion #1 for guidance as to when to perform a transabdominal ultrasound and saline or gel contrast. If saline or gel contrast is performed at Screening, it should also be performed at Week 24.
r. Obtain sample with a pipelle. Endometrial biopsy is performed at Screening 1 visit and Week 24 Visit and submitted to the central laboratory.
s. Procedure not required at the Early Termination Visit in patients whose last dose of study drug was during Week 6 or earlier. The procedure may be done if it will aid in the evaluation of an ongoing adverse event

t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results will be available prior to randomization. Schedule the test at or shortly after the Screening 1 visit. Bone densitometry should be completed prior to the Screening 3 visit and as early as possible to ensure results are available prior to randomization.
u. Patient paper diary: Patients enter diary information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit. Patient eDiary: Ensure that eDiary data collection begins at least 7 days prior to Day 1. Patients enter eDiary information on a daily basis for their compliance with (study treatment starting at Baseline/Day 1), menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening 3 visit and compliance with study treatment starting at Baseline/Day 1 through Week 24 or Early Termination.
v. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which

are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotropin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies (including 1 in women with uterine fibroids and 1 in women with endometriosis) have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least 1 dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations of estradiol in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

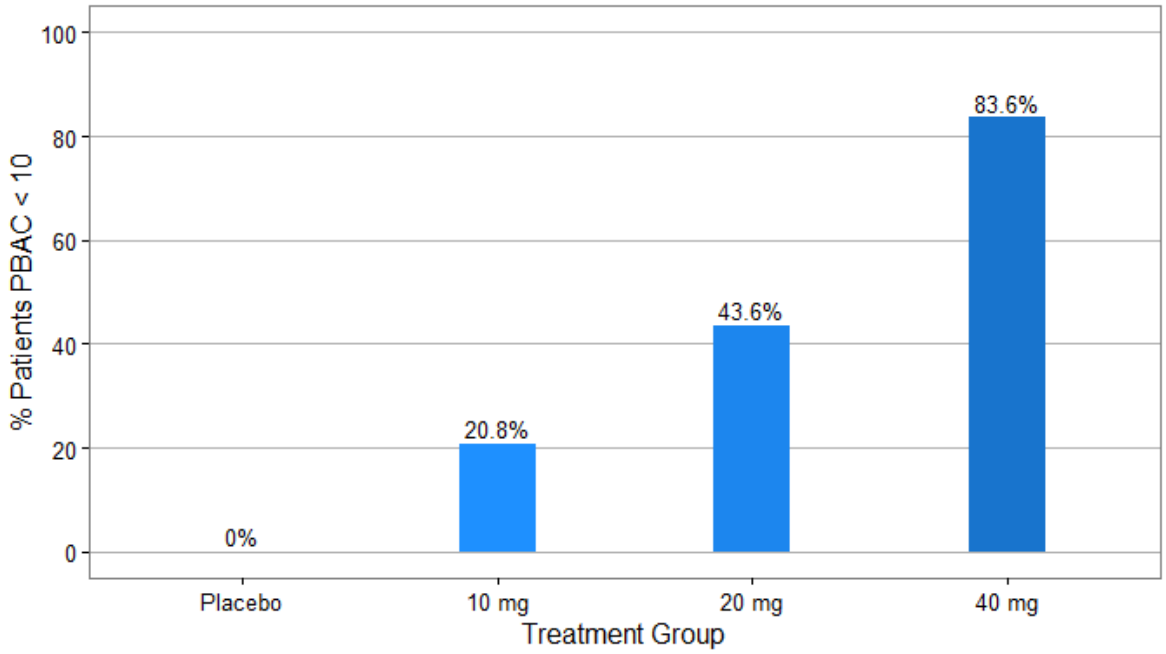
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 19%. The exposure of relugolix is increased by inhibitors

of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 final analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤ 50 ng/dL) and maintained these levels through at least 24 weeks. These 24-week data were comparable to testosterone levels achieved by leuprolide 22.5 mg administered by injection every 3 months. Study C27003 also demonstrated rapid and sustained suppression of testosterone levels by relugolix for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
Primary Efficacy	
• To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by

Objective(s)	Endpoint(s)
	the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks.	• Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.

Objective(s)	Endpoint(s)
Pharmacokinetic and Pharmacodynamic	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.
Exploratory	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or the placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by a centrally-reviewed transvaginal ultrasound (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or

≥ 160 mL for 1 cycle collected during the screening period. During the randomized treatment period, study participants will take blinded study drug orally once daily for 24 weeks. Women with iron-deficient microcytic anemia with a hemoglobin ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at the Screening visit. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24, followed by a repeat endometrial biopsy. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Samples will also be collected for PK assessment of relugolix, estradiol, and norethindrone, and for the pharmacodynamic assessment of LH, FSH, estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit to assess safety approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits are provided in Figure 4-2.

Figure 4-1 MVT-601-3001 Study Schematic

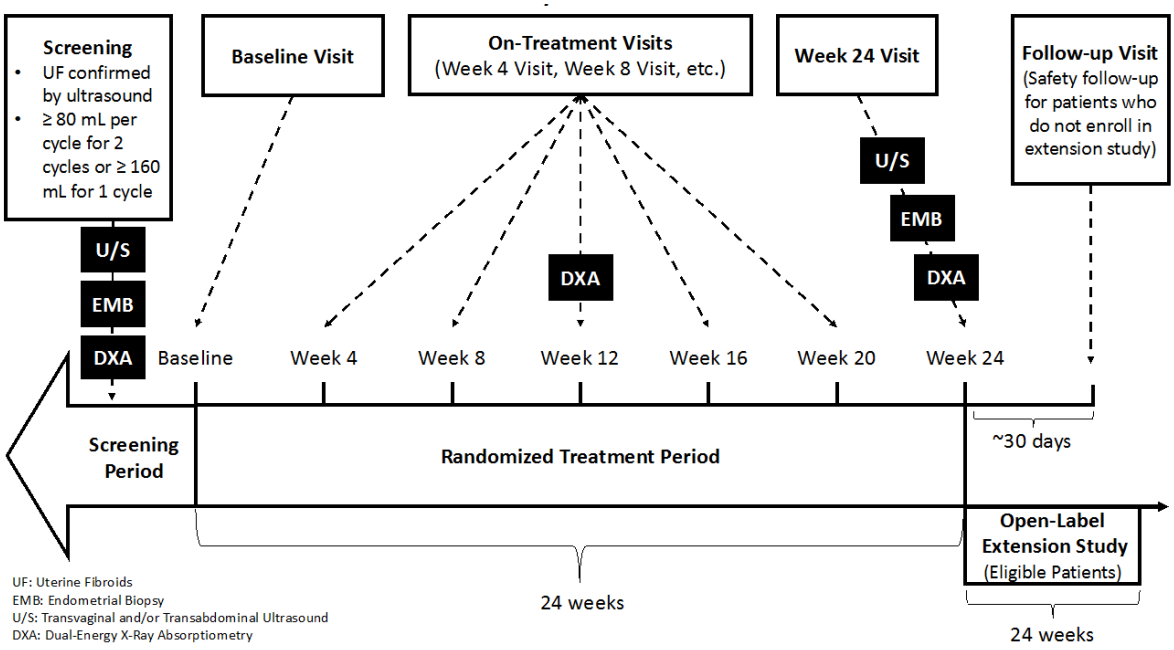


Figure 4-2 Schematic of MVT-601-3001 Screening Visit Scenarios

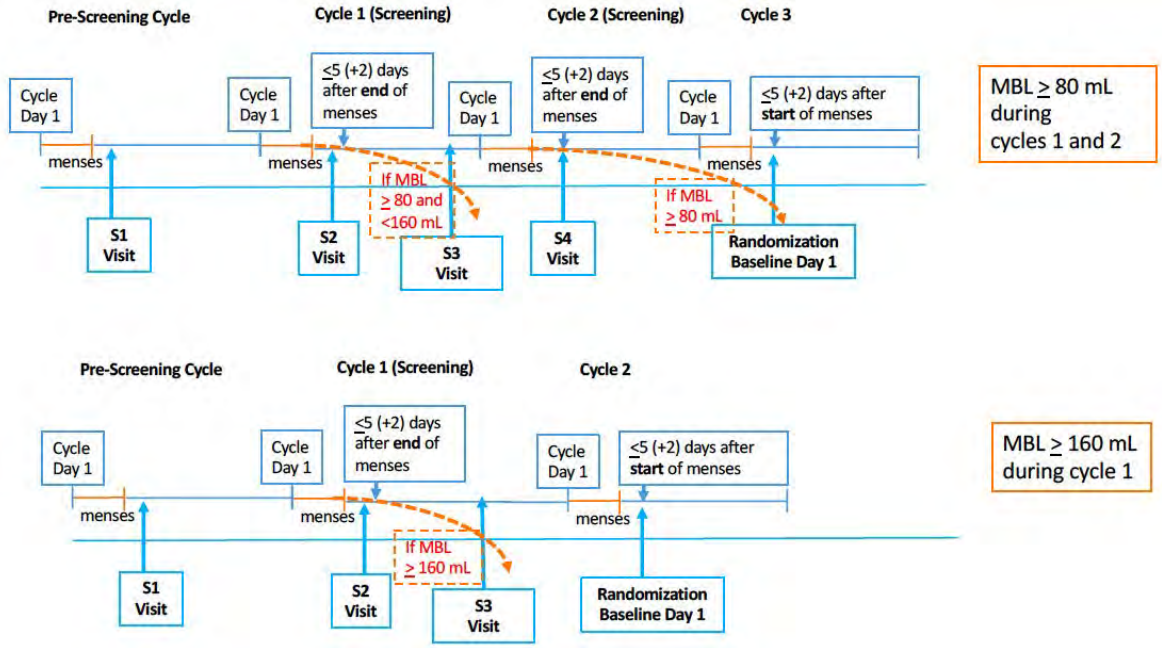


Figure 4-2

Screening visit 1 may be conducted at any time during the pre-screening cycle.

Top scenario:

- Eligibility is based on 2 consecutive screening cycles, each with ≥ 80 mL of menstrual blood loss assessed by the alkaline hematin method where the first screening cycle menstrual blood loss is also < 160 mL.

Bottom scenario:

- Eligibility is based on first screening cycle with ≥ 160 mL menstrual blood loss assessed by the alkaline hematin method.
- Patients whose first screening cycle MBL is < 80 mL and whose second screening cycle menstrual blood loss is ≥ 160 mL will follow the bottom scenario visit schedule.

Additional Scenarios (not depicted):

- Patients whose first screening cycle menstrual blood loss is < 80 mL and whose second screening menstrual blood loss is ≥ 80 mL but < 160 mL may collect menstrual blood loss during a third screening cycle if the first collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is ≥ 80 mL but < 160 mL and whose second screening menstrual blood loss is < 80 mL may collect menstrual blood loss during a third screening cycle if the second collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is < 80 mL may collect menstrual blood loss during a second cycle if the first collection was believed to be inadequate in a highly motivated patient. If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule.

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This study will focus on the primary objective of demonstrating a reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study is designed to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An extension study is planned to provide additional safety and efficacy data through 48 weeks.

Women with uterine fibroids and heavy menstrual blood loss by the alkaline hematin method of ≥ 80 mL/cycle for two cycles or ≥ 160 mL in one cycle during screening will be enrolled in this study. Randomization will be 1:1:1. Placebo was selected as the appropriate control for the study because there is no standard of care medical therapy for the long-term treatment of women with uterine fibroids and heavy menstrual bleeding. Commonly-used treatment options range from combined oral contraceptive pills, which are not effective in many cases, levonorgestrel-containing intrauterine devices, and leuprolide therapy indicated for 3 months in the preoperative setting.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. This dose was selected for evaluation in phase 2 clinical studies based upon phase 1 data demonstrating similar estradiol and progesterone suppression in women treated with single doses of relugolix 40 mg or 80 mg, and data demonstrating that premenopausal women treated with multiple doses of 40 mg once daily relugolix over 14 days had estradiol levels suppressed to a median value of 3.68 pg/mL.

Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, as described above, a phase 2 study of doses of relugolix 10, 20 and 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not

provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 48 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 48 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 1992; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the US as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate has demonstrated that this dose of add-back therapy maintains serum estradiol in the 25-50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy and is not included as a control arm as it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in a well-designed

large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study will primarily assess the efficacy and safety of relugolix 40 mg co-administered with a low-dose of estradiol and norethindrone acetate compared with placebo at 24 weeks to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes. An additional arm with monotherapy relugolix administered for 12 weeks followed by 12 weeks of relugolix co-administered with low-dose hormonal add-back therapy is included to provide data on the requirement for hormonal therapy to mitigate the adverse relugolix side effects of bone mineral density loss and hot flushes.

All eligible women who complete the 24-week study will be offered the opportunity to enroll in an open-label extension study to obtain long-term safety and efficacy data over an additional 28 weeks of treatment, providing approximately 1 year of safety data on the women originally randomized to relugolix.

4.3. Selection of Study Population

The study population will include approximately 390 premenopausal women aged 18 to 50 years with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for randomization and enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Baseline Day 1 visit, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;

4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

    Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

    Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone.
5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently, the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion;
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;

10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;

18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

4.5. Method of Assigning Patients to Treatment Group and Patient ID Number

After a patient is screened, the investigator determines that the patient is eligible for enrollment, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient's Baseline Day 1 visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient Identification Number.

4.6. Removal of Patients from Therapy

Completion of the Week 24 defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;

- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of dual contraception are:

- Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 2 months following the last dose of study drug.

A patient may start hormonal contraception 4 weeks after her last study dose of study drug provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including just prior to receiving first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

Each patient will be instructed to take one tablet and one capsule per day.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, and color. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

Table 5-1 Description of MVT-601-3001 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An Swedish orange, over-encapsulated round film-coated white tablet with placebo back-fill material	A Swedish orange capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients.

Placebo to match relugolix is a pink tablet using common excipients.

The fixed-dose combination tablet of estradiol 1.0 mg and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3001 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with relugolix placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule for 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state (other than water) in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

On clinic days, patients should be instructed not to eat or drink (other than water) prior to their clinic visit if the appointment is in the morning. If the appointment is later in the day, patients should not eat for at least 2 hours before the appointment and should also not to eat or drink (other than water) for at least 1 hour after administration of the study drug.

Patients should take any oral iron supplementation with meals.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 35°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix, the estradiol/norethindrone acetate combination, relugolix placebo, and the estradiol/norethindrone acetate placebo to be distributed will meet all applicable requirements of the US FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Relugolix 40 mg and relugolix placebo will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate or estradiol/norethindrone acetate placebo.

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding by the investigator for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient’s individual study treatment, however, the investigator should make every effort to first contact the medical monitor or appropriate study

personnel to discuss options **before** unblinding the patient's treatment assignment. If unblinding by the investigator occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient. Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment.

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and prior to each visit, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused and used study drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zolendronic acid	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	1 month

Drug Class	Examples	Window/Comments
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone	2 months (6 months for depot subcutaneous or intramusclar injections)
Estrogens	estradiol valerate conjugated estrogens	2 months (6 months for depot subcutaneous or intramusclar injections)
Oral Contraceptives	combined or progestin only	1 month for patients reporting a typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	1 week
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	No prior use if used for reduced bone mineral density
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin tranexamic acid vitamin k preparations factor Xa inhibitors	1 month

Drug Class	Examples	Window/Comments
Glucocorticoids	prednisolone or prednisone dexamethasone	No window Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (≤ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	carbamazepine rifampin St John's wort	2 weeks Patients requiring a short course of these drugs during the study must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporin diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole lopinavir/ritonavir quercetin quinidine ranolazine ticagrelort verapamil	2 weeks (6 months for amiodarone) Patients requiring a short course of these drugs during the study must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

From the Screening 1 visit to the Week 24 (or Early Termination) visit, the recommended analgesics for uterine-fibroid associated pain are as follows:

- First-line: ibuprofen
- Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
- Third-line: opioid or opioid-acetaminophen combination
- Fourth-line: investigator discretion

The purpose of these recommendations is to standardize, to the extent possible, analgesic medication use to facilitate the effects on the secondary endpoint regarding of uterine-fibroid-related pain.

Patients should be instructed not to use analgesics for prophylactic purposes.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL but ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.7. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities in the study synopsis (see Section 1.1). The study is divided into three periods: screening period, randomized treatment period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study; unscheduled visits may also occur as needed to evaluate patients).

6.2. Screening Period

Patients should have a diagnosis of uterine fibroids and a history of heavy menstrual bleeding with or without associated pain on a background of generally regular menses (ie, regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next menstrual period) as reported by the patient for at least 3 months prior to the Screening 1 visit.

The screening period consists of the Screening 1, 2, 3, and 4 visits.

See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening. The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.

6.2.1. Screening 1 Visit

The Screening 1 visit will be conducted following the signing of the informed consent form and may occur at any time during the menstrual cycle. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications, study procedure-related adverse events and any serious adverse events. In addition, vital signs, height, weight, temperature, a complete physical examination, gynecology examination, ultrasound, endometrial biopsy, Papanicolaou test (if needed), clinical laboratory tests, urinalysis, and a urine pregnancy test will be done. Feminine products will be dispensed with instructions to collect and return all products used during the next menses. The paper diary will also be dispensed at this visit and should be completed daily starting with this visit. The bone mineral density scan and mammogram should be scheduled at this time (or within a few days of this visit). Bone densitometry should be scheduled to be prior to the Screening 3 visit and as early as feasible to ensure results are available prior to randomization.

The order of procedures should be as follows. Patients not meeting eligibility criteria after any procedure should not undergo subsequent procedures.

- Medical history and review of prior uterine imaging studies
- Review of concomitant medications (including supplements and over the counter medications)
- Review of inclusion and exclusion criteria
- Urine pregnancy test
- Vital signs, weight, and height

- Ultrasound – do not proceed with additional procedures if no uterine fibroids are identified with the local/initial reading
- Gynecology examination, Papanicolaou test (if need), endometrial biopsy
- Clinical laboratory tests, urinalysis
- Dispense feminine products and paper diary with instructions to begin recording starting information daily, starting on the Screening 1 visit day
- Schedule mammogram (if needed)
- Schedule bone densitometry

The ultrasound will be a transvaginal ultrasound (with or without a transabdominal ultrasound (see Section 4.3 ultrasound entry criteria), performed to assess for uterine fibroids. Saline or gel contrast may be used but is not required (see Section 4.3 ultrasound entry criteria). The anatomic location and size of the fibroid disease will be estimated by the local reader. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to randomization). The investigator, rather than the central reader, will determine if any exclusionary pathology is present. If ultrasound fails to demonstrate fibroids on the local reading, do not proceed with additional Screening visit 1 procedures.

The Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit and the specimen is to be submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

The endometrial biopsy will be obtained using a pipelle and submitted to the Central Laboratory.

The mammogram must be done in patients ≥ 39 years of age by the time of the (anticipated) Baseline Day 1 visit if there is no record (and reading) from within 6 months prior to the screening period.

6.2.2. Screening 2 Visit

Screening 2 visit is scheduled to occur within 5 (+2) days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine products. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine products will be dispensed for collection of menstrual blood loss during the next menses. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be obtained as an unscheduled test. Women whose laboratory testing reveals iron-deficiency anemia as defined in the study must be started on iron therapy.

Confirm the scheduling of the bone densitometry and mammogram (if needed) and review mammogram results, if available. The mammogram must be normal (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) in order for the patient to be eligible.

Once the menstrual blood loss results from the first cycle are available, schedule Screening 3 visit as soon as feasible and within 5 (+2) days of receiving results showing that the menstrual blood loss is ≥ 80 mL.

Patients will be dispensed feminine products to be gathered for the second cycle.

6.2.3. Screening 3 Visit

The patient will return for the Screening 3 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL and within ≤ 15 days after the Screening 2 visit. At the Screening 3 visit, review of inclusion and exclusion criteria will be conducted confirmation of continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. At this visit, review the endometrial biopsy results and review mammogram results, if available. Confirm that the bone densitometry scans have been submitted for central reading. The mammogram and central bone densitometry results must be available prior to randomization.

6.2.4. Screening 4 Visit

The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle. If not skipped, then the Screening 4 visit is scheduled to occur within 5 (+2) days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn for hemoglobin assessment. The patient's eDiary data collection will be reviewed. Laboratory and imaging evaluations will be reviewed to ensure eligibility for randomization.

6.2.5. Menstrual Blood Loss Repeat Collection

At the discretion of the investigator, the collection of menstrual blood loss can be repeated once during the screening period (either after the first or second screening cycle) if one menstrual cycle does not meet the heavy menstrual bleeding alkaline hematin criteria and it is thought to be due to an inadequate collection by a highly motivated patient.

6.2.6. Re-Screening

Patients who fail screening may be re-screened with approval of the medical monitor. Patients undergoing re-screening will sign a new informed consent form and issued a new screening number. For patients who begin re-screening within 10 weeks of signing the original informed consent form, transvaginal ultrasound, endometrial biopsy, and bone densitometry do not need to be repeated, if performed previously.

6.3. Randomized Treatment Period (Baseline to Week 24)

At the Baseline Day 1 visit, patients will be randomized to one of the three study treatment arms (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the Week 24 visit. Patients will continue recording daily in their eDiary. On-treatment study visits will occur every 4 weeks through the end of Week 24. At each post-baseline visit, patients will return their feminine products for alkaline hematin testing. Safety monitoring including signs and symptoms directed physical examination, waist circumference, ECGs, clinical laboratory tests, pregnancy tests, and

adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12 and Week 24 visits. A repeat transvaginal ultrasound (with or without a transabdominal ultrasound) and endometrial biopsy will be performed at the Week 24 visit. The endometrial biopsy will be read centrally. Study drug and eDiary compliance will be reviewed at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the randomized treatment period.

Sites should try to schedule patient visits during the morning, instructing patients to arrive before taking their study drug to allow for pre-dose PK/pharmacodynamic sampling. Patients must come to the clinic in the fasted state (eg, nothing to eat or drink other than water after midnight the day before the clinic visit) for the Baseline Day 1 and Week 24/Early Termination visits.

For visits other than Baseline Day 1 and Week 24/Early Termination, if the clinic visit cannot be scheduled for the morning, patients may eat in the morning but should not have eaten or had anything to drink other than water for at least 2 hours prior to the clinic visit and must not eat or drink (other than water) for at least 1 hour after the clinic visit. In these situations, the laboratory requisitions must indicate that the patient was not fasted for their chemistry and lipid testing.

6.4. Continuation into Extension Study

It is expected that most patients will enter the 28-week extension study (MVT-601-3003), which will be conducted under a separate protocol. Patients will provide separate informed consent to participate in the extension study during which all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate.

6.5. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 24 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 24; however, for patients whose last dose of study drug is during Week 6 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound), endometrial biopsy, and bone densitometry. These procedures may be performed, however, at the investigator's discretion, if they aid in follow-up of ongoing adverse events.

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3003), will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation. Patients who withdraw early from this study will also undergo the Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Refer to the Schedule of Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, PK and pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.7. Study Procedures

6.7.1. Efficacy-Related Procedures

6.7.1.1. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.7.1.2. Transvaginal and Transabdominal Ultrasound

Transvaginal with or without transabdominal ultrasound with or without saline or gel contrast is performed for the diagnosis of uterine fibroids, to determine uterine and myoma volumes, and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Transvaginal ultrasound will be performed. Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = D1 x D2 x D3 x π / 6
Where:
D1 = the longest diameter of the myoma or uterus (unit of length: cm)
D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

6.7.1.3. Endometrial Biopsy

An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A pipelle should be used to obtain the specimen. A second biopsy is to be performed at the Week 24 visit. The biopsies will be read centrally.

6.7.1.4. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.7.1.5). To maintain blinding, concentrations of these hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.7.1.5. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping

procedures are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.7.1.6. Patient Diary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. Patients will complete daily eDiaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will be reviewed by the investigator to identify any potential adverse events.

Patients will also receive a paper diary to enter information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit.

6.7.1.7. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 3). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the randomized treatment period. Patients will complete the MIQ at each visit at the site before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.8. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). Patients will complete the UFS-QoL questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.9. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale (EQ-5D) is a standardized instrument for use as a measure of health outcomes (see Appendix 5). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued,

6.7.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one sample of blood will be collected and stored for future pharmacogenomic analyses. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.7.2. Safety-Related Procedures

6.7.2.1. Weight, Height, Waist Circumference, and Body Mass Index

Patients should have weight and height measured while wearing indoor clothing and with shoes removed. Waist circumference should be measured with a measuring tape wrapped around the narrowest portion of the patient’s mid-section.

6.7.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.7.2.3. Physical and Gynecologic Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. Visual acuity will be checked at the beginning and end of the study by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for women without an available test result from within 6 months prior to the Screening 1 visit and submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

6.7.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory. The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Creatinine kinase Hemoglobin A1c Creatine Kinase Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase	White Blood Cell (WBC) Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and Clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine Microscopy
	Lipids	**Pregnancy**
	Total Cholesterol Low Density Lipoprotein High Density Lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)
Hormones	**Serology**	**Iron Studies**
Thyroid-Stimulating Hormone Intact Parathyroid Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Vitamin D [25(OH)D]	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody	Iron Ferritin

A separate sample will be collected at the Day 1 visit in all patients and will be banked for hepatitis serology (Table 6-1) in all patients. The samples will be analyzed, if requested, by the medical monitor for evaluation of abnormal liver tests during the study.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, serology, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory or laboratories used.

6.7.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.7.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient). Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual subject will be monitored by a central radiology laboratory over the course of the study. Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the sties assessed during the study. In this case, repeat scan may be required for confirmation of the results, and it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.

Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of blood collected for pharmacogenomics testing (see Section 6.7.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her

sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), ECGs, bone mineral density assessments, endometrial biopsy results, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are 'intermittent'. All other events are 'continuous'. Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted, however, study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events which jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local Institutional Review Board (IRB) or Institutional Ethics Committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's eDiary entries and answers to the UFS-QoL will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Study procedure-related adverse events will be collected from the signing of the informed consent form.

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit approximately 30 days after the last dose of study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

With the exception of adverse events that are considered related to study screening procedures, (which are to be recorded as adverse events), events occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized treatment period or the Follow-up visit should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet SAE criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the International Normalized Ratio (INR) > 1.5; or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
    - Hepatobiliary tract disease
    - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
    - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
    - Alcoholic hepatitis
    - Nonalcoholic steatohepatitis
    - Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a Safety Reporting Form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Serious Adverse Event report form and is as follows:

Send completed Safety Report Forms to PRA Safety & Risk Management:

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
North/South American sites:	PPD	PPD or PPD
Europe, Asia, Pacific and Africa sites:		PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest (AECI) reporting, please call:

- North/South America: PPD or PPD
- Europe, Asia, Pacific, and Africa: PPD

The initial report should include:

- Study number (MVT-601-3001)
- Site address and number
- Investigator name
- Patient ID number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity)
- Causal relationship to the study drug

If the patient died, the report should include the cause of death as the event term (with death as outcome) and whether or not the event leading to death was related to study drug treatment, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (ie, more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy reporting forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.7.2 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, electrocardiograms and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine fibroids. Low-dose hormonal add-back therapy with estradiol and norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (QTc prolongation), hepatic enzyme increases, PLD, reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, osteopenia, metabolic bone disease, and prior medical therapy for low bone mineral density.	Bone mineral density will be monitored at the Baseline Day 1, Week 12, and End of Treatment visits and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-gp inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec.	12-lead ECG at Baseline Day 1, Week 12 and End of Treatment visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal LFTs are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal LFTs (AST or ALT > 3 x ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be checked at the beginning and end of the study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	Clinical chemistries assessing LFTs, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% across primary and secondary endpoint testing will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL.

Statistical analyses for all efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations. The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;

- Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method;
- Time to amenorrhea as measured by the by the alkaline hematin method;
- Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities;
- Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;
- Change from Baseline to Week 24 in uterine volume; and
- Change from Baseline to Week 24 in uterine fibroid volume.

The analysis methods used for the primary endpoint will be applied to the analyses of the secondary endpoints of proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment compared between relugolix Group B and placebo Group C, the proportion of patients with amenorrhea over the last 35 days, the proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of at least 1 g/dL at Week 24 and the proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume and time to amenorrhea, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions and stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline. The between treatment comparisons will be performed using model derived least squares means with treatment, stratification factors, baseline result accounted for in the model.

Baseline Numerical Rating Scale score is defined as the average Numerical Rating Scale score from the 35 days of data collected prior to the date of first dose of study drug after randomization. The Numerical Rating Scale score during the final study month is the average Numerical Rating Scale score during the last 35 days on treatment.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment group as treated. The treatment emergent period will be defined as the period of time from the first dose date of study drug through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 12.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each parameter.

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. ECGs will also be read centrally. The distributions of corrected QT interval will be summarized at each visit. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for average of L1-L4, total hip, and femoral neck. All data will be listed and summarized by visit. The change, percent change from Baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

All data will be listed and summarized by visit. The change, percent change from baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by treatment arm.

The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar, total hip, or femoral neck) will be estimated with 95% confidence intervals by treatment group. Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.5. Pharmacokinetic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed:

- Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively;
- Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational

new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the IB, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the IB, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
    - Patient identification (name, date of birth, gender);
    - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
    - Participation in the study (including study number);
    - Study discussed and date of informed consent;
    - Dates of all visits;
    - Documentation that protocol-specific procedures were performed;
    - Results of efficacy parameters, as required by the protocol;

- Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
- Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
- Concomitant medication (including start and end date); and
- Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and

placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publically Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 90 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 120 days in order to obtain patent protection if deemed necessary.

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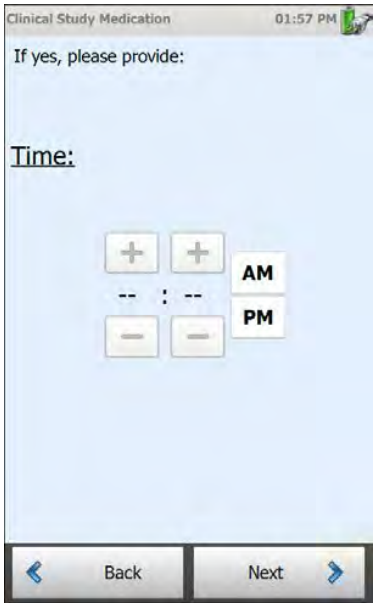
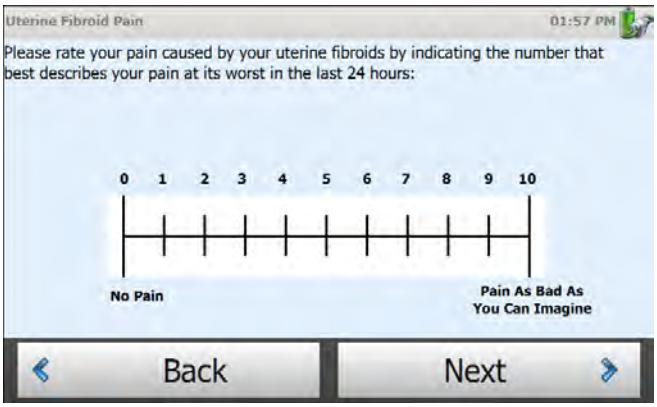
APPENDICES

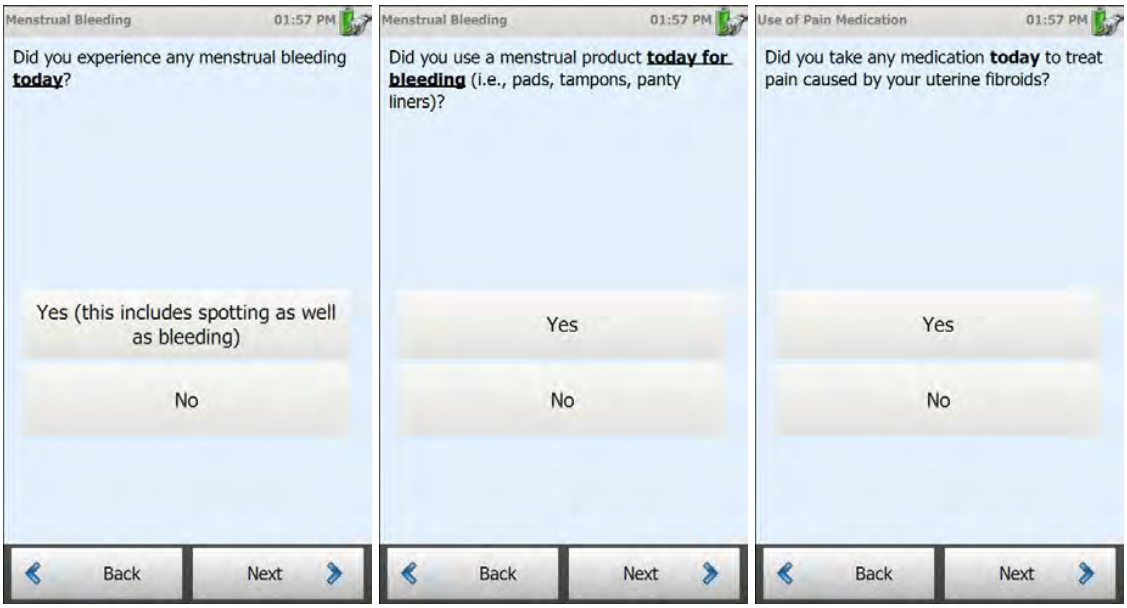
Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

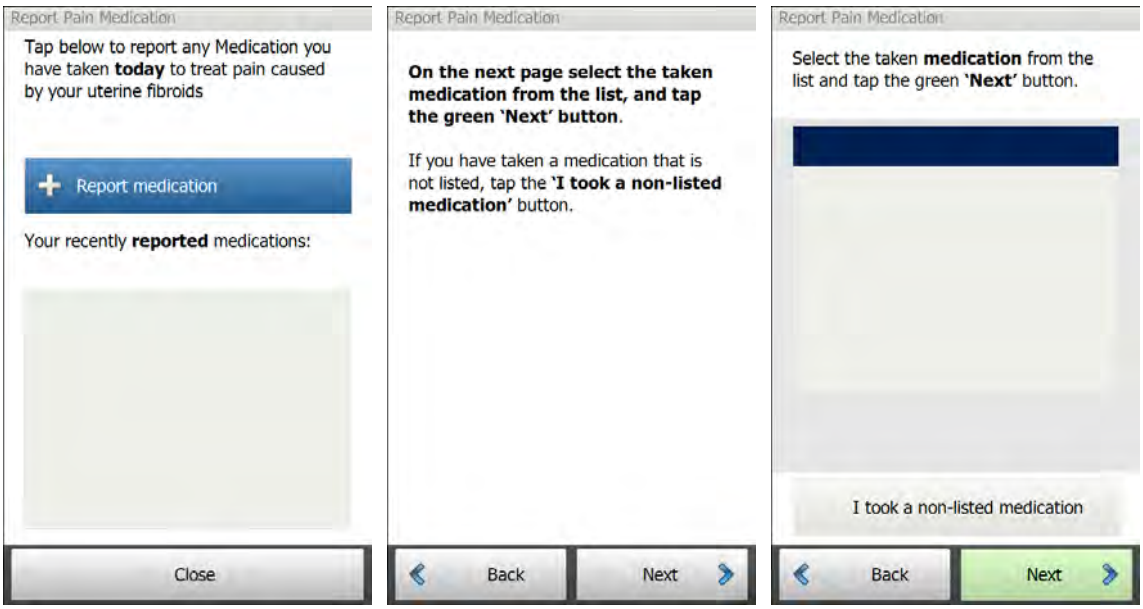
Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

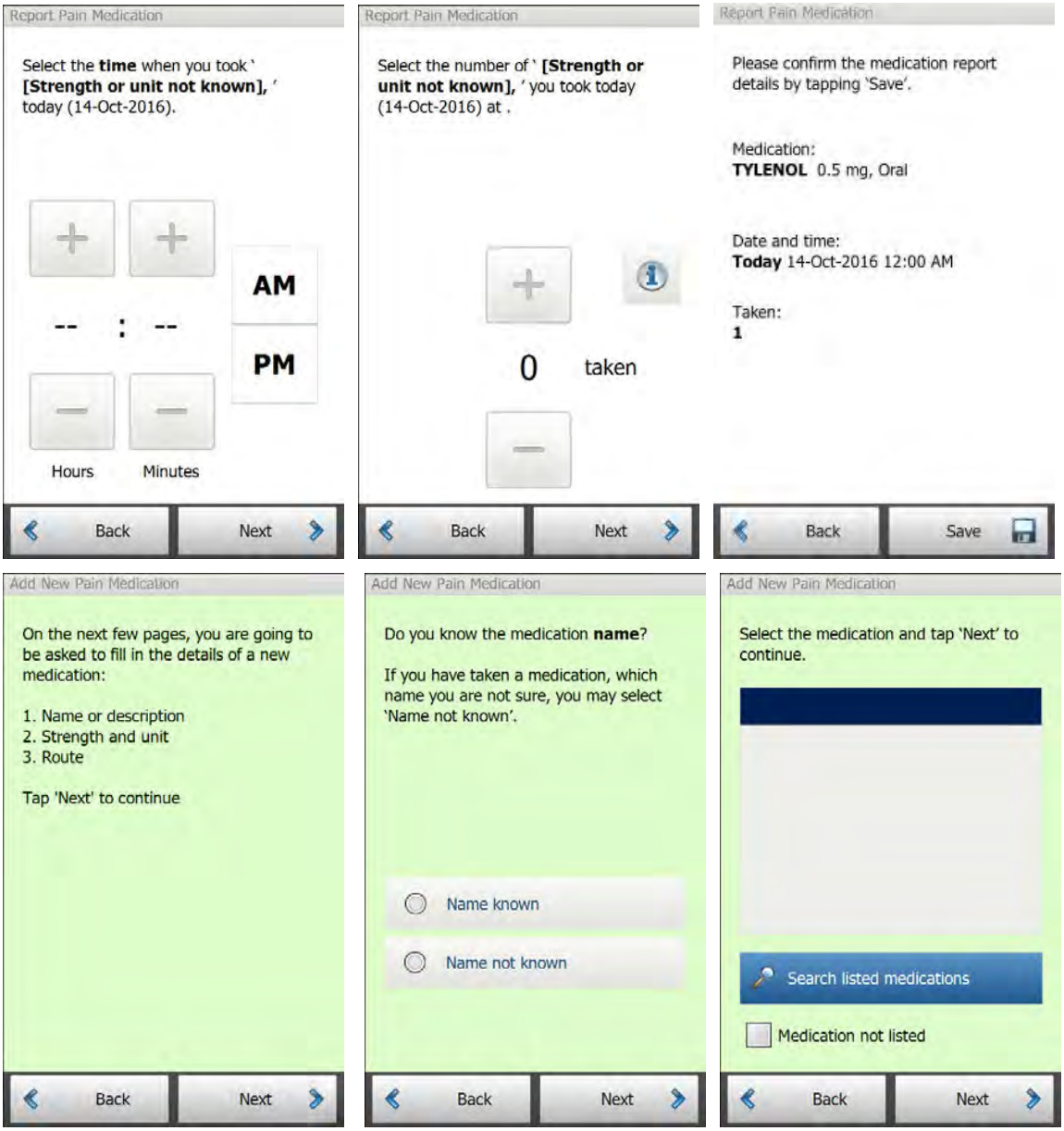
Appendix 2. Daily eDiary

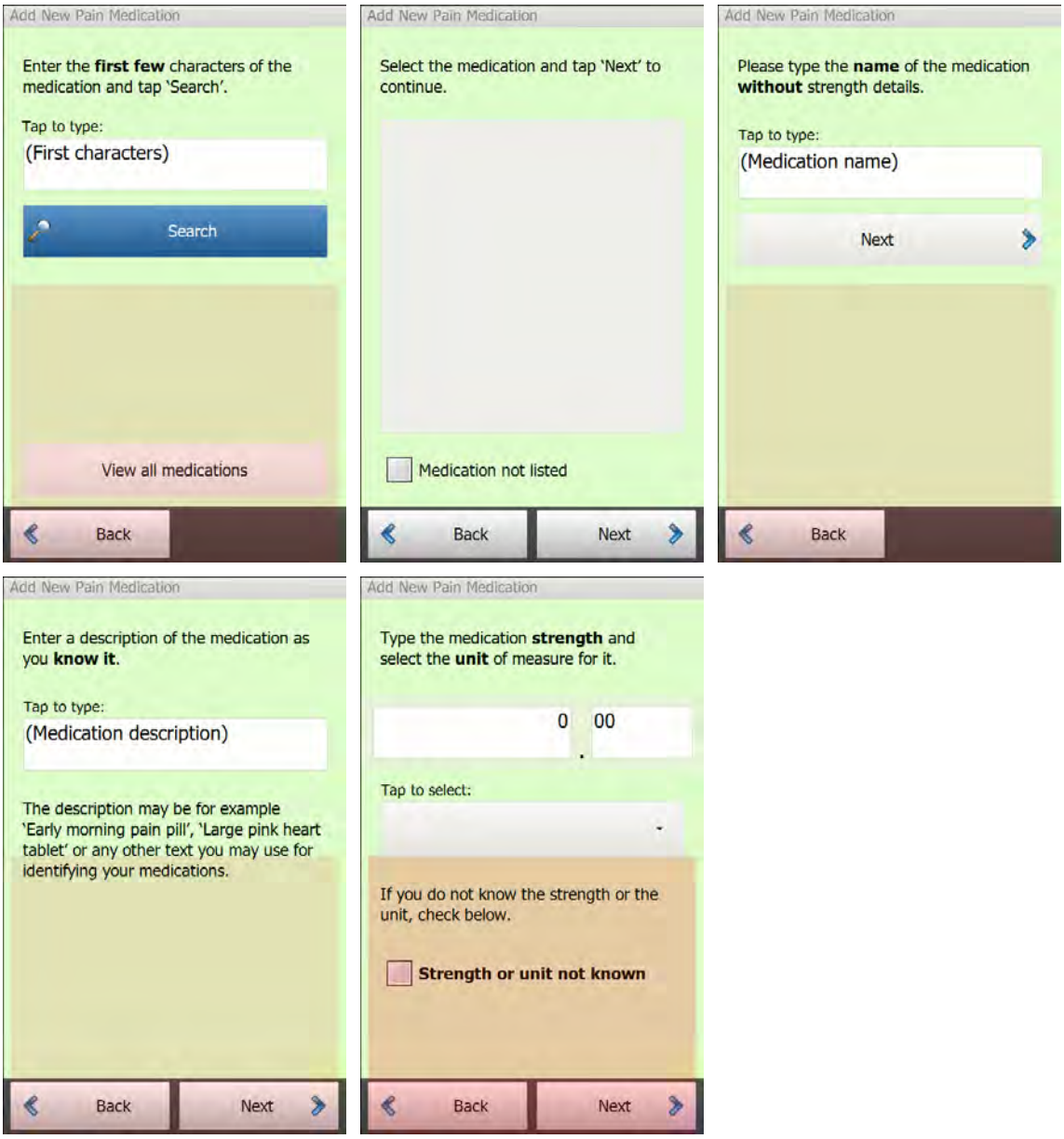


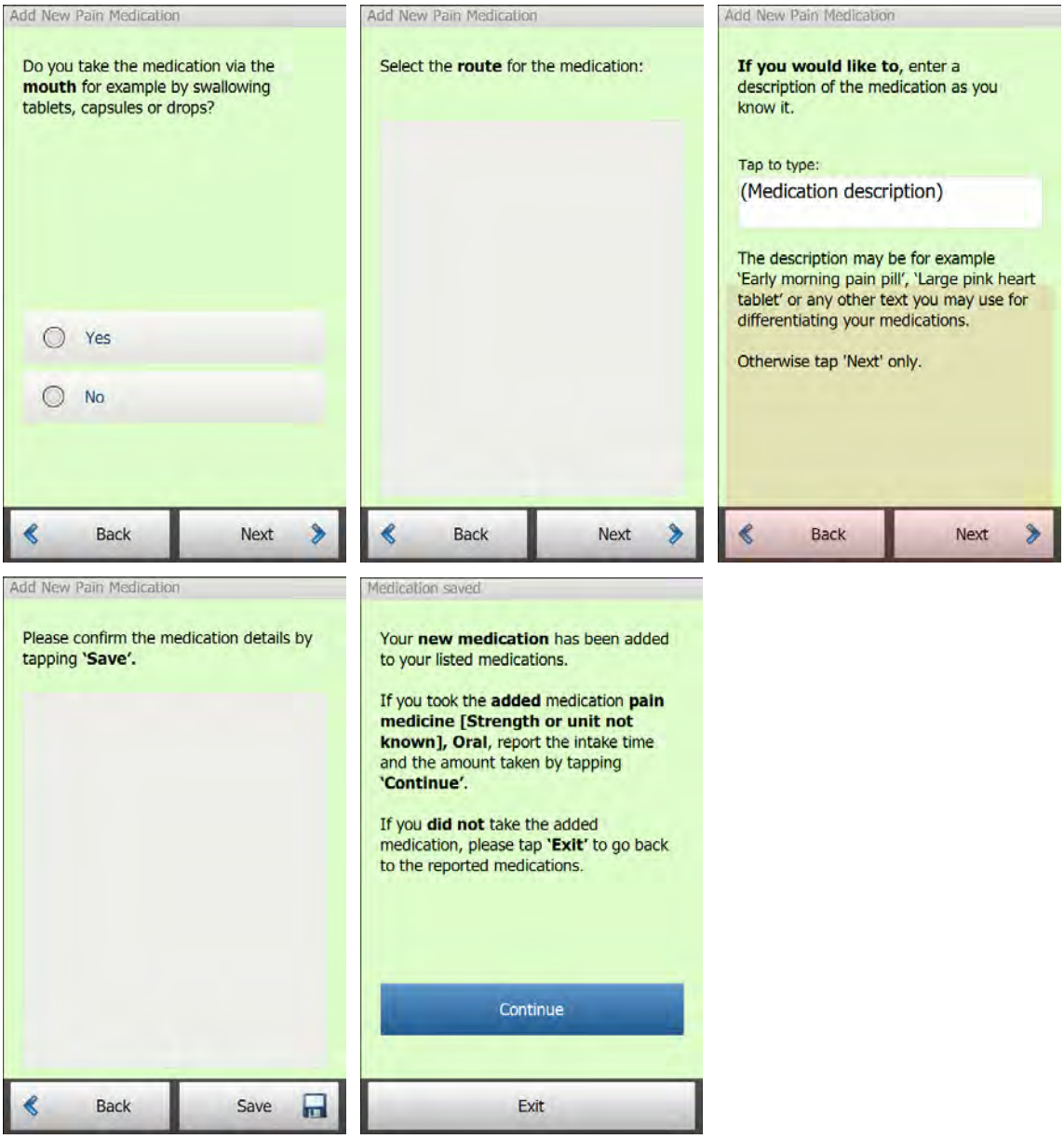



Menstrual Bleeding
01:57 PM
Did you experience any menstrual bleeding **today**?
Yes (this includes spotting as well as bleeding)
No
Back
Next
Menstrual Bleeding
01:57 PM
Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?
Yes
No
Back
Next
Use of Pain Medication
01:57 PM
Did you take any medication **today** to treat pain caused by your uterine fibroids?
Yes
No
Back
Next


Report Pain Medication
Tap below to report any Medication you have taken **today** to treat pain caused by your uterine fibroids
Report medication
Your recently **reported** medications:
Close
Report Pain Medication
On the next page select the taken medication from the list, and tap the green 'Next' button.
If you have taken a medication that is not listed, tap the **'I took a non-listed medication'** button.
Back
Next
Report Pain Medication
Select the taken **medication** from the list and tap the green **'Next'** button.
I took a non-listed medication
Back
Next


Report Pain Medication
Select the time when you took ' [Strength or unit not known], ' today (14-Oct-2016).
AM
PM
-- : --
Hours
Minutes
Back
Next
Report Pain Medication
Select the number of ' [Strength or unit not known], ' you took today (14-Oct-2016) at .
0 taken
Back
Next
Report Pain Medication
Please confirm the medication report details by tapping 'Save'.
Medication:
TYLENOL 0.5 mg, Oral
Date and time:
Today 14-Oct-2016 12:00 AM
Taken:
1
Back
Save
Add New Pain Medication
On the next few pages, you are going to be asked to fill in the details of a new medication:
1. Name or description
2. Strength and unit
3. Route
Tap 'Next' to continue
Back
Next
Add New Pain Medication
Do you know the medication name?
If you have taken a medication, which name you are not sure, you may select 'Name not known'.
Name known
Name not known
Back
Next
Add New Pain Medication
Select the medication and tap 'Next' to continue.
Search listed medications
Medication not listed
Back
Next


Add New Pain Medication
Enter the first few characters of the medication and tap 'Search'.
Tap to type:
(First characters)
Search
View all medications
Back
Add New Pain Medication
Select the medication and tap 'Next' to continue.
Medication not listed
Back
Next
Add New Pain Medication
Please type the name of the medication without strength details.
Tap to type:
(Medication name)
Next
Back
Add New Pain Medication
Enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for identifying your medications.
Back
Next
Add New Pain Medication
Type the medication strength and select the unit of measure for it.
0
00
Tap to select:
If you do not know the strength or the unit, check below.
Strength or unit not known
Back
Next


Add New Pain Medication
Do you take the medication via the **mouth** for example by swallowing tablets, capsules or drops?
Yes
No
Back
Next
Add New Pain Medication
Select the **route** for the medication:
Back
Next
Add New Pain Medication
If you would like to, enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for differentiating your medications.
Otherwise tap 'Next' only.
Back
Next
Add New Pain Medication
Please confirm the medication details by tapping **'Save'.**
Back
Save
Medication saved
Your **new medication** has been added to your listed medications.
If you took the **added** medication **pain medicine [Strength or unit not known], Oral**, report the intake time and the amount taken by tapping **'Continue'.**
If you **did not** take the added medication, please tap **'Exit'** to go back to the reported medications.
Continue
Exit

Appendix 3. Menorrhagia Impact Questionnaire

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

Pt. Initials: _____ **Pt. ID:** _____

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Made you anxious about traveling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Interfered with your physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Caused you to feel tired or worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Made you feel as if you are not in control of your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Made you concerned about soiling underclothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Made you feel less productive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Made you feel self-conscious of weight gain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Made you feel that it was difficult to carry out your usual activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Interfered with your social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Made you feel conscious about the size and appearance of your stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Made you concerned about soiling bed linen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐	☐	☐	☐	☐
24. Made you feel down hearted and blue?	☐	☐	☐	☐	☐
25. Made you feel wiped out?	☐	☐	☐	☐	☐
26. Caused you to be concerned or worried about your health?	☐	☐	☐	☐	☐
27. Caused you to plan activities more carefully?	☐	☐	☐	☐	☐
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐	☐	☐	☐	☐
29. Caused you embarrassment?	☐	☐	☐	☐	☐
30. Made you feel uncertain about your future?	☐	☐	☐	☐	☐
31. Made you feel irritable?	☐	☐	☐	☐	☐
32. Made you concerned about soiling outer clothes?	☐	☐	☐	☐	☐
33. Affected the size of clothing you wear during your periods?	☐	☐	☐	☐	☐
34. Made you feel that you are not in control of your health?	☐	☐	☐	☐	☐
35. Made you feel weak as if energy was drained from your body?	☐	☐	☐	☐	☐
36. Diminished your sexual desire?	☐	☐	☐	☐	☐
37. Caused you to avoid sexual relations?	☐	☐	☐	☐	☐

3

Appendix 5. European Quality of Life Five-Dimension Five-Level Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

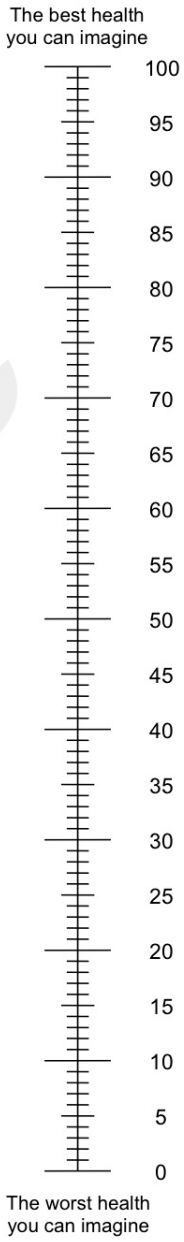
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6. Assessment of Abnormal Liver Function Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with low-dose estradiol and norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Appendix Table 1[a]; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • CBC with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.; • Serology for celiac disease; • Appropriate liver imaging; • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

CLINICAL STUDY PROTOCOL

Study Title:	An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
IND #:	131161
Version:	Original
Effective Date:	10-NOV-2016

SPONSOR SIGNATURE PAGE

An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3001

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

10Nov2016
Date

10 Nov 2016
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
EQ-5D	European Quality of Life Five-Dimension Five-Level
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menstrual Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart

Term	Explanation
PD	pharmacodynamics
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
USP/NF	United States Pharmacopeia and the National Formulary
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3001
Location	Multinational, including North and South America, Europe, and Australia
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	<u>Primary Efficacy Objective</u> • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. <u>Secondary Efficacy Objectives</u> • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate
	Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.

Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (~11 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal and/or transabdominal ultrasound. Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL each cycle for 2 cycles during the screening period. During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transvaginal and/or transabdominal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy. Patients will have paired baseline and end-of-treatment endometrial biopsies, independent of ultrasound results. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients

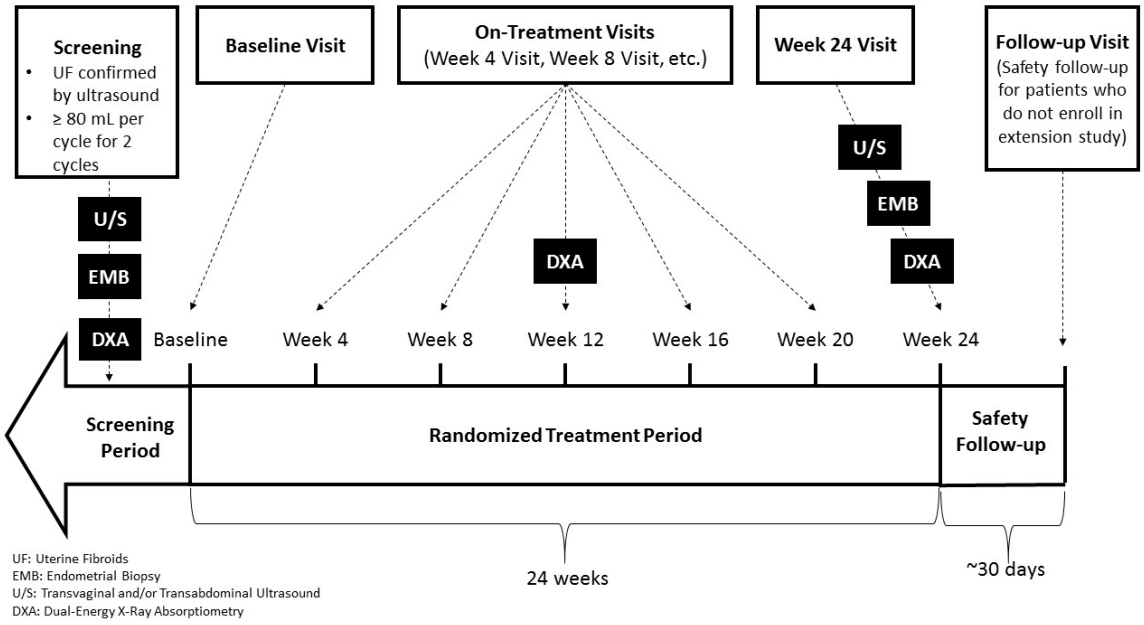
will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

Study Schematic



Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);
4. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
5. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal

ultrasound performed with saline or gel contrast during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
   a. Subserosal, intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter), or
   b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3;
6. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period;
7. Patient does not desire and is not expected to be a candidate for gynecological surgery or ablation procedures within the 6 months following enrollment;
8. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
9. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently during any required washout for excluded medications (if applicable), the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
10. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer);
11. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period;
12. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment;
2. Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine or total hip;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;

7. Has a history of the use of bisphosphonates, calcitonin/calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Calculated creatinine clearance < 60 mL/min using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina;
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at

any screening visit or the Baseline Day 1 visit; h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram; 15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit; 16. Has a history of clinically significant condition(s) including, but not limited to the following: a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded); b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma; c. History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year); 17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study; 18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable washout periods from these medications are also described therein); 19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form); 21. Has participated in a previous clinical study that included the use of relugolix; 22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling); 23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.	
Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, color, and odor for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, color, and odor will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, color, and odor.

Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. <u>Primary Efficacy Endpoint</u> • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume. Safety Endpoints • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.

	Exploratory Endpoints • Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of 260 (130 patients in each of the relugolix and placebo arms) will provide $> 99\%$ power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be

presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE, version 5.0. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4),), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3001

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)	**Within 4 days after completion of menses**	**Within 4 days after completion of Screening 1 menses**	**Within 10 days of Screening 2 visit**	**Within 4 days after completion of 2nd Screening menses**	**Within 4 days of the start of menses**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X	X
Height	X												
Weight	X				X						X	X	X
Temperature	X				X						X	X	
Adverse Event Collection[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination, Including Visual Acuity[g]	X				X						X		
Gynecologic Examination with Pap Test, if applicable			X[h]								X		

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X	X
12-Lead Electrocardiogram			X		X			X			X	X	X
Clinical Laboratory Tests[l]	X	X			X[i, j]	X	X	X	X	X	X[i, k]	X[l]	X
PK Sample[m]					X	X		X			X	X[l]	
PD Sample[n] and Administer Dose of Study Drug in Clinic	X				X	X	X	X	X	X	X		X
PGx Sample[o]					X								
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X		
Urinalysis	X				X								
Mammogram[p]			X										
Transvaginal or Transabdominal Ultrasound[q]			X								X		
Endometrial Biopsy[r]			X								X[s]		
Bone Densitometry[t]			X					X			X		
Randomization[u]					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X			
Dispense Study Treatment					X	X	X	X	X	X			
Patient eDiary[v]			X	X	X	X	X	X	X	X	X		
Feminine Product Collection and Venous Blood Sample[w]		X		X		X	X	X	X	X	X		
MIQ					X	X	X	X	X	X	X		
UFS-QoL					X			X			X		
EQ-5D					X						X		
Treatment Compliance						X	X	X	X	X	X	X	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Status of Menstruation Recovery													X

Notes:

Abbreviations: EQ-5D, European Quality of Life Five-Dimension Five-Level Scale; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; UFS-QoL, Uterine Fibroid Score – Quality of Life

a. The screening period should be initiated after the informed consent form is signed and any required washout for excluded medications or devices is complete.
b. Visit to occur within 4 days of the completion of menses.
c. Visit to occur within 10 days after Screening 2 visit if the menstrual blood loss is determined to be ≥ 80 mL. The Screening 1 or Screening 2 visits for alkaline hematin menstrual blood loss may be repeated at the discretion of the investigator if one menstrual cycle does not meet MBL criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 4 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose PD sample, pregnancy and urinalysis test samples prior to first dose of study drug. The patient must complete MIQ, UFS-QoL, and EQ-5D questionnaires prior to first dose of study drug.
e. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003), a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~4 weeks after an Early Termination visit).
f. Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.
g. Complete Physical Exam (not including a gynecological examination). Visual acuity must be assessed with a standard eye chart. The patient should wear any prescription glasses or contacts during the assessment.
h. Papanicolaou test must be conducted for women without a test result 6 months prior to the Screening 1 visit. Re-measurement should be performed for inadequate or false-positive results.
i. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state for the Baseline and Week 24 visit clinical laboratory tests.
j. At the Baseline Day 1 visit (clinical laboratory tests in fasted state), in addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, iron, ferritin, and hemoglobin A1c. An additional sample will be collected at this visit and stored for possible future testing for presence of hepatitis A, B, and C if required per request from medical monitor to assess etiology of liver test abnormalities.
k. At the Week 24 visit or Early Termination visit (clinical laboratory tests in fasted state), in addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.

l. For an Unscheduled visit, a central safety laboratory assessment or PK sample collection is performed as needed.
m. Pharmacokinetics samples: Samples should be obtained in the fasted since study drug is administered on an empty stomach. Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics sample collections are complete (with the exception of Week 24 when no dose is administered).
n. Pharmacodynamic samples: Samples should be obtained in the fasted since study drug is administered on an empty stomach, collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Instruct the patient not to take her study treatment at home on these visit days. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Screening 1 visit, Week 24 and Follow Up visits when no dose is administered).
o. Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive)
p. Patients ≥ 39 years of age at the time of the Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period; if not, schedule at the Screening 3 visit.
q. Transvaginal or transabdominal ultrasound with saline or gel contrast must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps. Results must be submitted to and confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is the preferred procedure. A transabdominal ultrasound may also be obtained if indicated, for example, by extension of large masses outside the pelvis.
r. Endometrial biopsy is performed at Screening after the first acceptable alkaline hematin sample collection.
s. Endometrial biopsy is to be performed at the Week 24 visit and may be requested for central review if abnormal.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results available prior to randomization.
u. Randomization: After a patient is screened and the investigator determines that the patient is eligible for randomization the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the Study Reference Manual. The sponsor (or designee) will approve the patient's randomization in writing. Once the site has received approval, the patient may undergo her Baseline Day 1 visit.
v. Patient electronic diary: Patients enter diary information on a daily basis for their compliance with (study treatment starting at Baseline/Day 1), menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening visit 2 and compliance with study treatment starting at Baseline/Day 1 through Week 24 or early termination.
w. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which

are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotrophin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 µg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 µg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 µg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥100 mg/kg (estimated C_{max} of 4.0 µg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 µg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and three phase 2 studies (including one in women with uterine fibroids and two in women with endometriosis) have been completed. In addition, six clinical studies evaluating relugolix are ongoing, including two phase 1 studies, two phase 2 studies in men with prostate cancer (US and Europe), and two phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least one dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

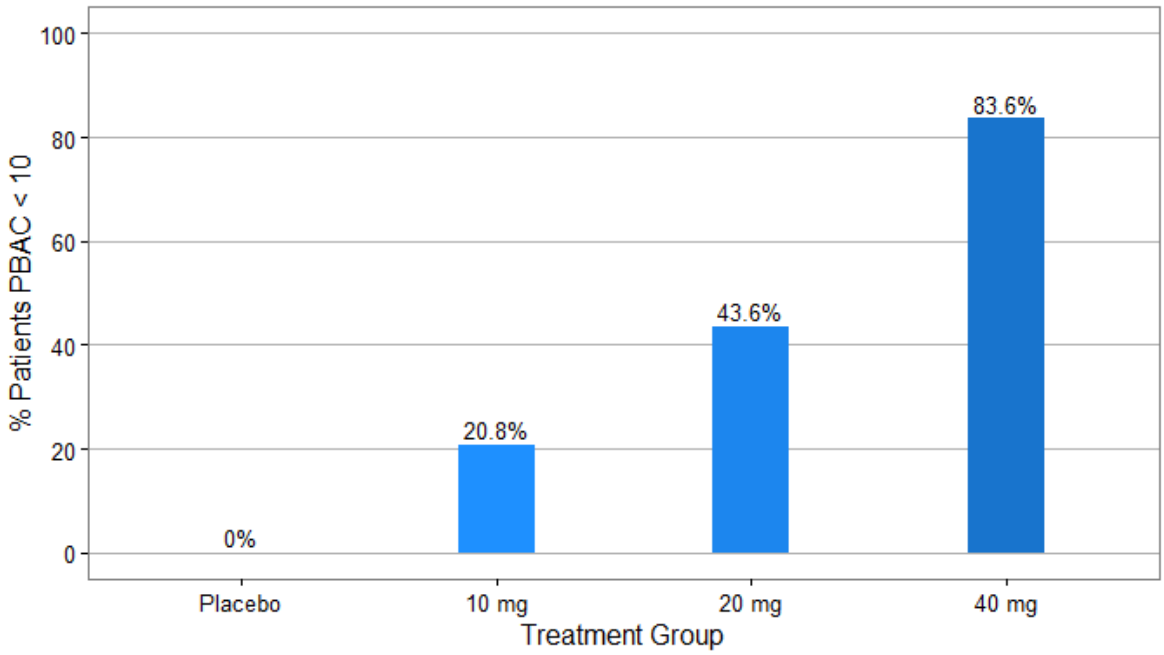
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 45%. The exposure of relugolix is increased by inhibitors

of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver function test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 interim analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤50 ng/dL) and maintained these levels through at least 24 weeks. These data are comparable to testosterone levels achieved by leuprolide 22.5 mg every 3 months. Study C27003 demonstrated rapid and sustained suppression of testosterone levels for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, Version 9.0, dated 09 November 2016, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
Primary Efficacy	
• To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by

Objective(s)	Endpoint(s)
	the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks.	• Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.
<u>Pharmacokinetic and Pharmacodynamic</u>	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-

Objective(s)	Endpoint(s)
low-dose estradiol and norethindrone acetate.	dose concentrations of LH, FSH, estradiol, and progesterone.
Exploratory	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or the placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (~11 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by a centrally-reviewed transvaginal and/or transabdominal ultrasound. Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for each of 2 cycles during the screening period. During the randomized treatment period, study participants will take blinded study drug orally once daily for 24 weeks. Women with iron-deficient microcytic anemia with a hemoglobin ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline and Week 24 visits, patients will attend visits monthly (ie, every

4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transvaginal and/or transabdominal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Samples will also be collected for PK assessment of relugolix, estradiol, and norethindrone, and for the pharmacodynamic assessment of LH, FSH, estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit to assess safety approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits and dispensation and collection of feminine products during this time are provided in Figure 4-2.

Figure 4-1 MVT-601-3001 Study Schematic

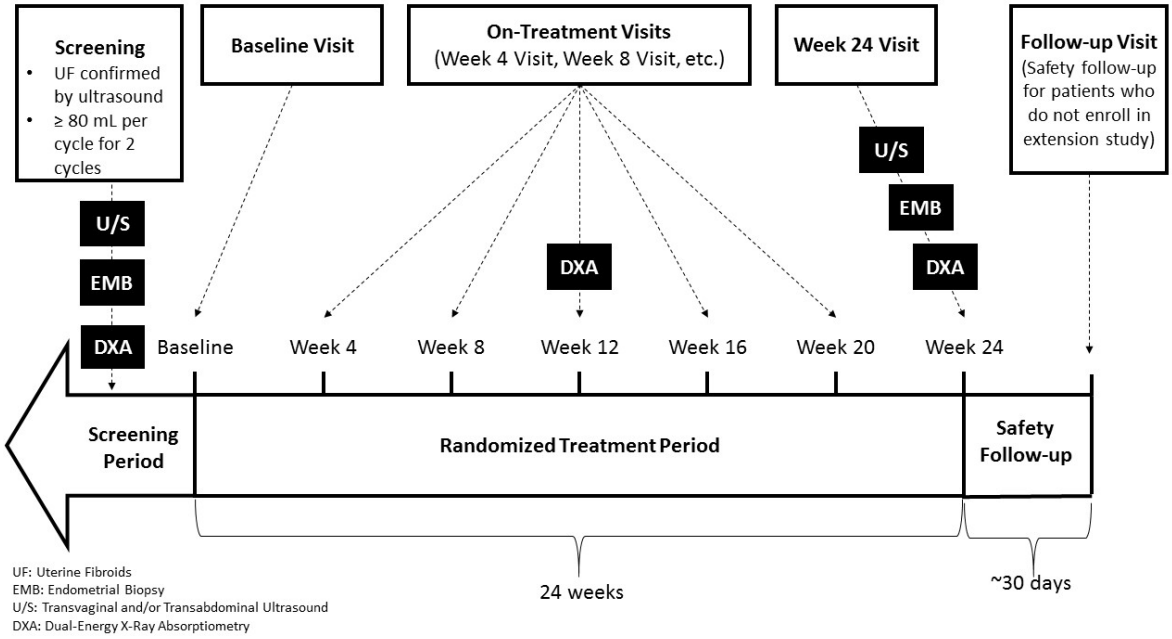
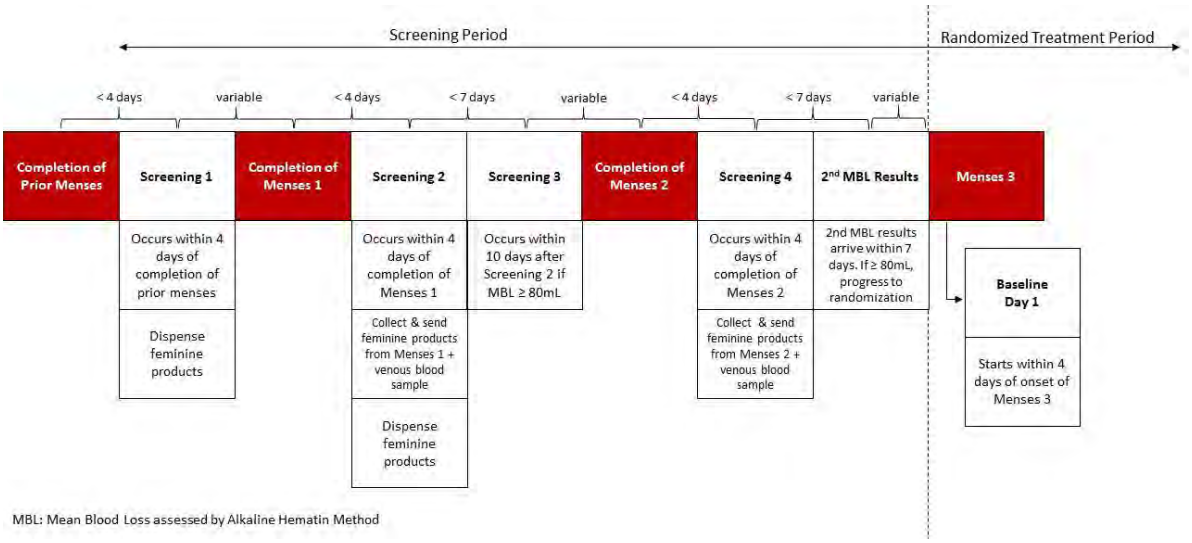


Figure 4-2 Schematic of MVT-601-3001 Screening Visits and Feminine Product Dispensation and Collection during the Screening Period



4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This study will focus on the primary objective of demonstrating a reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study is designed to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An extension study is planned to provide additional safety and efficacy data through 48 weeks.

Women with uterine fibroids and heavy menstrual blood loss by the alkaline hematin method of ≥ 80 mL/cycle as assessed during two cycles will be enrolled in this study. Randomization will be 1:1:1. Placebo was selected as the appropriate control for the study because there is no standard of care medical therapy for the long-term treatment of women with uterine fibroids and heavy menstrual bleeding. Commonly-used treatment options range from combined oral contraceptive pills, which are not effective in many cases, levonorgestrel-containing intrauterine devices, and leuprolide therapy indicated for 3 months in the preoperative setting.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. This dose was selected for evaluation in phase 2 clinical studies based upon phase 1 data demonstrating similar estradiol and progesterone suppression in women treated with single doses of relugolix 40 mg or 80 mg, and data demonstrating that premenopausal women treated with multiple doses of 40 mg once daily relugolix over 14 days had estradiol levels suppressed to a median value of 3.68 pg/mL.

Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, as described above, a phase 2 study of doses of relugolix 10, 20 and 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to

move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 48 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 48 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 1992; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the US as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate has demonstrated that this dose of add-back therapy maintains serum estradiol in the 25-50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet; Activella US Prescribing Information, 2013) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy and is not included as a control arm as it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral

density loss unacceptable for long-term treatment. This phase 3 study will primarily assess the efficacy and safety of relugolix 40 mg co-administered with a low-dose of estradiol and norethindrone acetate compared with placebo at 24 weeks to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes. An additional arm with monotherapy relugolix administered for 12 weeks followed by 12 weeks of relugolix co-administered with low-dose hormonal add-back therapy is included to provide data on the requirement for hormonal therapy to mitigate the adverse relugolix side effects of bone mineral density loss and hot flushes.

All eligible women who complete the 24-week study will be offered the opportunity to enroll in an open-label extension study to obtain long-term safety and efficacy data over an additional 24 weeks of treatment, providing approximately 1 year of safety data on the women originally randomized to relugolix.

4.3. Selection of Study Population

The study population will include approximately 390 premenopausal women aged 18 to 50 years with heavy menstrual bleeding (≥ 80 mL over 2 cycles by the alkaline hematin method) associated with uterine fibroids demonstrated over two cycles during the screening period.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for randomization and enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Baseline Day 1 visit, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);
4. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
5. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal ultrasound performed with saline or gel contrast during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3;

6. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period;
7. Patient does not desire and is not expected to be a candidate for gynecological surgery or ablation procedures within the 6 months following enrollment;
8. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
9. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently during any required washout for excluded medications (if applicable), the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
10. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer);
11. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period;
12. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment;
2. Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine or total hip;

6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin/calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Calculated creatinine clearance < 60 mL/min using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina;
    c. History of congestive heart failure;

d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;
h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram;

15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year);
17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable washout periods from these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

4.5. Method of Assigning Patients to Treatment Group and Patient ID Number

After a patient is screened and the investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the Study Reference Manual. The sponsor (or designee) will approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient's Baseline Day 1visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient Identification Number.

4.6. Removal of Patients from Therapy

Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);

- Patients who have percent change from Baseline in bone mineral density at either the Week 12 or Week 24 visit (or any unscheduled visit) at the lumbar spine (average L1-L4), total hip, or femoral neck of < -4.0 that is repeated and confirmed (ie, both values are < -4.0);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.6 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of dual contraception are:

- Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the

requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 1 month following the last study visit.

A patient may start hormonal contraception 4 weeks after her last study visit provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including just prior to receiving first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

Each patient will be instructed to take one tablet and one capsule per day.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, color, and odor. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

Table 5-1 Description of MVT-601-3001 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An over-encapsulated round film-coated white tablet with placebo back-fill material	Capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 12 or 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™).

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the United States Pharmacopeia and the National Formulary (USP/NF) excipients.

Placebo to match relugolix is a pink tablet using USP/NF excipients.

The fixed-dose combination tablet of estradiol 1.0 mg and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient USP/NF grade back-fill material.

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3001 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with relugolix placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

Patients should take any oral iron supplementation with meals.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK/PD samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse

event. Patients may subsequently be re-started on study drug, with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 1°C to 30°C until it is used or returned to the sponsor (or designee). A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix, the estradiol/norethindrone acetate combination, relugolix placebo, and the estradiol/norethindrone acetate placebo to be distributed will meet all applicable requirements of the US FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Relugolix 40 mg and relugolix placebo will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate or estradiol/norethindrone acetate placebo.

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient's individual study treatment, however, the Investigator should make every effort to first contact the medical monitor or appropriate study personnel to discuss options **before** unblinding the patient's treatment assignment. If unblinding occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient, unless that information is important for the safety of patients currently in the study. Patients whose treatment assignment has been unblinded will be permanently discontinued from treatment.

The sponsor (or designee) **may** unblind the treatment assignment for any patient with a serious adverse event.

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and prior to each visit, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused stud drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

This table provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Washout Periods

Drug Class	Examples	Washout Period/Comments
Bisphosphonates	alendronate etidronate	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	1 month
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone	2 months (6 months for depot subcutaneous or intramusclar injections)

Drug Class	Examples	Washout Period/Comments
Estrogens	estradiol valerate conjugated estrogens	2 months (6 months for depot subcutaneous or intramusclar injections)
Oral Contraceptives	combined or progestin only	2 months
Selective Estrogen Receptor Modulators	raloxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	2 months
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin, calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	2 months
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin tranexamic acid vitamin k preparations	1 month
Glucocorticoids	prednisolone or prednisone dexamethasone	No washout Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction Short duration ($\leq$ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	carbamazepine rifampin St John's wort	2 weeks

Drug Class	Examples	Washout Period/Comments
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporin diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole lopinavir/ritonavir quercetin quinidine ranolazine ticagrelort verapamil	2 weeks (6 months for amiodarone)

Abbreviation: GnRH, gonadotropin-releasing hormone

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

Use of analgesics is **ONLY permitted under the following conditions** from the Screening 1 visit to the Week 24 (or Early Termination) visit:

- Ibuprofen or other non-steroidal anti-inflammatory medications can be used as the first choice medicine for pain **associated with uterine fibroids**. Narcotic analgesics should be used for severe pain that cannot otherwise be controlled.
- Acetaminophen can be used as the first choice medicine for treatment of an adverse event or other pain **NOT associated with uterine fibroids** such as headache or a common cold.
- Analgesics for topical/external use are also permitted.
- Codeine that is not intended to relieve pain associated with uterine fibroids (eg, codeine phosphate in a combination cold remedy) is permitted.

This restriction was set because analgesic medications are likely to have an impact on the evaluation of a secondary endpoint regarding pain. Analgesics refer to drugs containing compounds that have indications for pain symptoms in the package inserts and antispasmodic drugs that possess indications for gynecological or urological disease in the package inserts.

Patients should be instructed not to use analgesics for prophylactic purposes. Patients should also be instructed to record in the eDiary their worst pain symptoms during the past 24 hours before taking analgesics.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL but ≤ 10 g/dL, a mean corpuscular volume below normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.7. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities in the study synopsis (see Section 1.1). The study is divided into three periods: screening period, randomized treatment period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study; unscheduled visits may also occur as needed to evaluate patients).

6.2. Screening Period

Pre-screening evaluation, not including any study procedures or tests, may be conducted prior to the initial formal screening evaluation at the Screening 1 visit in an effort to identify patients unlikely to meet study-related entry criteria. Review of medical history, menstrual history, and prior uterine imaging assessments is permitted. Patients should have a diagnosis of uterine fibroids and a history of heavy menstrual bleeding with or without associated pain on a background of generally regular menses (ie, regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next cycle) as reported by the patient for at least 3 months prior to the Screening 1 visit.

The screening period consists of the Screening 1, 2, 3, and 4 visits. See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening.

The Screening 1 visit will be conducted following the signing of the informed consent form and should occur within 4 days after completion of menses. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications and SAEs, obtaining of clinical evaluations including vital signs, height, weight, temperature, a complete physical examination including visual acuity (not including a gynecological examination), clinical laboratory tests, urinalysis, and a urine pregnancy test will be conducted. Feminine product will be dispensed with instructions to collect and return all product used during the next menses.

Screening 2 visit is scheduled to occur within 4 days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine product to determine if their menstrual blood loss is ≥ 80 mL. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine product will be dispensed for collection of menstrual blood loss during the next menses.

The patient will return for the Screening 3 visit within 10 days of Screening 2 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL. At the Screening 3 visit 3, review of inclusion and exclusion criteria will be conducted confirmation of continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. In addition, the patient will undergo a gynecological examination (a Papanicolaou test must be conducted for women without a test result 6 months prior to the Screening 1 visit). Re-measurement should be performed for inadequate or false-positive results. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. A transvaginal and/or transabdominal pelvic ultrasound with saline or gel contrast will be performed to assess for uterine fibroids. The anatomic location and size of the fibroid disease will be estimated. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to randomization). An endometrial biopsy will be obtained. Bone densitometry by DXA of the lumbar spine, total hip, and femoral neck will be scheduled to be completed prior to randomization for submission to central reader. Patients who will be ≥ 39 years of age at the time of the Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) within 3 months prior to the Screening 1 visit. If not, a mammogram will also be scheduled as a part of Screening 3 visit.

Patients will be provided with the eDiary instructions at this Screening 3 visit and will be dispensed feminine products to be gathered for the second cycle. Each patient will begin recording information into the eDiary including menstrual bleeding and use of feminine products for menstrual bleeding (ie, on the day of Screening 3 visit). The eDiary will be maintained on a daily basis for the duration of the study up until the day before the Week 24 (or Early Termination) visit.

The Screening 4 visit is scheduled to occur within 4 days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be

collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn for hemoglobin assessment. The patient's eDiary data collection will be reviewed. Laboratory and imaging evaluations will be reviewed to ensure eligibility for randomization.

At the discretion of the investigator, the Screening 1 or 2 visits can be repeated if one menstrual cycle does not meet the heavy menstrual bleeding alkaline hematin criteria and it is thought to be due to an inadequate collection by a highly motivated patient. A Randomization Authorization Form must be submitted to the sponsor for approval prior to conducting the Baseline Day 1 visit. The Baseline Day 1 visit should be scheduled to coincide as closely as possible to when the patient will be finished with her next menses.

6.3. Randomized Treatment Period (Baseline to Week 24)

At the Baseline Day 1 visit, patients will be randomized to one of the three study treatment arms (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the Week 24 visit. Patients will continue recording daily in their eDiary. On-treatment study visits will occur every 4 weeks through the end of Week 24. At each post-baseline visit, patients will return their feminine products for alkaline hematin testing. Safety monitoring including signs and symptoms directed physical examination, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12 and 24 visits. A repeat transabdominal and/or transabdominal ultrasound and endometrial biopsy will be performed at the Week 24 visit. The endometrial biopsy will be read locally. Study drug and eDiary compliance will be reviewed at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the randomized treatment period.

Sites should try to schedule patient visits during the morning, instructing patients to arrive before taking their study drug to allow for pre-dose PK/PD sampling. Patients should come to the clinic in the fasted state (eg, nothing to eat or drink after midnight the day before the clinic visit).

6.4. Continuation into Extension Study

It is expected that most patients will enter the 24-week extension study (MVT-601-3003), which will be conducted under a separate protocol. Patients will provide separate informed consent to participate in the extension study during which all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate.

6.5. Follow-up Visit

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3003), will have a Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation. Patients who withdraw early from this study will also undergo the Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another

investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Refer to the Schedule of Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits conducted to evaluate adverse events: vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment and PK sample if indicated, 12-lead ECG, recording of concomitant medications, and study drug compliance.

6.7. Study Procedures

6.7.1. Efficacy-Related Procedures

6.7.1.1. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.7.1.2. Transvaginal and/or Transabdominal Ultrasound

Transvaginal and/or transabdominal ultrasound with saline or gel contrast is performed for the diagnosis of uterine fibroids, to determine uterine and myoma volumes, and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single physician (investigator or sub-investigator) will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Transvaginal ultrasound is preferred, but transabdominal ultrasound may be used as necessary for full visualization of the uterus. The ultrasound method used at screening should be repeated for the ultrasound at the Week 24 visit.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = D1 x D2 x D3 x π / 6
Where:
D1 = the longest diameter of the myoma or uterus (unit of length: cm)
D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

6.7.1.3. Endometrial Biopsy

An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A second biopsy is to be performed at the Week 24. The biopsies will be read locally, but biopsies may be requested for central review.

6.7.1.4. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.7.1.5). To maintain blinding, concentrations of these hormones should be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.7.1.5. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping

procedures are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.7.1.6. Patient eDiary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. During menstruation, patients will complete daily diaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will act as its own source data and these data will be reviewed by the investigator to identify any potential adverse events.

6.7.1.7. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 3). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the randomized treatment period. Patients will complete the MIQ at each visit at the site before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.8. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom – Quality of Life (UFS-QoL) score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). Patients will complete the UFS-QoL questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.9. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale (EQ-5D) is a standardized instrument for use as a measure of health outcomes (see Appendix 5). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued,

6.7.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one 5-mL sample of whole blood will be collected and stored for future pharmacogenomic analyses. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.7.2. Safety-Related Procedures

6.7.2.1. Weight, Height, and Body Mass Index

Patients should have weight and height measured while wearing indoor clothing and with shoes removed.

6.7.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.7.2.3. Physical and Gynecologic Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. Visual acuity will be checked at the beginning and end of the study by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for

women without an available test result from within 6 months prior to the Screening 1 visit. Re-measurement should be performed for inadequate or false-positive results.

6.7.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium	White Blood Cell (WBC) Count	Qualitative
Chloride	WBC Differential	Protein
Bicarbonate	Red Blood Cell Count	Glucose
Blood Urea Nitrogen	Hemoglobin	Occult blood
Creatinine	Hematocrit	Urobilinogen
Glucose	Mean Corpuscular Volume	Bilirubin
Calcium	Platelet Count	Pregnancy test
Phosphate		(human chorionic gonadotropin)
Magnesium		
Albumin		
Total Protein		
Alkaline Phosphatase		
Lactate Dehydrogenase		
Creatine Kinase		
Liver Function Tests including:		
Bilirubin Total		
Alanine Aminotransferase		
Aspartate Aminotransferase		
Gamma-Glutamyl Transferase		
Lipid Profile including:		
Total Cholesterol		
Low Density Lipoprotein		
High Density Lipoprotein		
Triglycerides		

Specialized Hormonal Assessments: Thyroid-Stimulating Hormone Parathyroid Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Iron (Baseline only) Ferritin ((Baseline only) Hemoglobin A1c (Baseline and Week 24 only)		

A separate sample will be collected at the Day 1 visit and will be banked and tested for presence of hepatitis A, B, and C (hepatitis A antibody, IgM, hepatitis B core antibody, IgM, hepatitis B surface antigen, and hepatitis C antibody) if requested by the medical monitor for evaluation of abnormal liver function tests.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory or laboratories used.

6.7.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.7.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient).

The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.

6.8. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of 5 mL of whole blood collected for pharmacogenomics testing (see Section 6.7.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), ECGs, bone mineral density assessments, endometrial biopsy results, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are 'intermittent'. All other events are 'continuous'. Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted, however, study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example,

drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events which jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local Institutional Review Board (IRB) or Institutional Ethics Committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's eDiary entries and answers to the UFS-QoL will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for

medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient or partner will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1).

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit approximately 30 days after the last dose of study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Any event occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained

by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE, version 5.0. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE Version 5.0

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized treatment period or the Follow-up visit should be reported to the sponsor using the Serious Adverse Event

Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet SAE criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the International Normalized Ratio (INR) >1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
   - Alcoholic hepatitis
   - Nonalcoholic steatohepatitis
   - Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a serious adverse event report form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.

The contact information for submission of serious adverse events and events of overdose or pregnancy is available on the Serious Adverse Event report form. Information may also be provided to PPD

The initial report should include:

- Study number (MVT-601-3001)
- Site name and number
- Investigator name
- Patient ID number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity)
- Causal relationship to the study drug

If the patient died, the report should include the cause of death and whether or not the cause of death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (ie, more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy reporting forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.7.2 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, electrocardiograms and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine

fibroids. Low-dose hormonal add-back therapy with estradiol and norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (QTc prolongation), hepatic enzyme increases, PLD, reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, osteopenia, metabolic bone disease, and prior medical therapy for low bone mineral density.	Bone mineral density will be monitored at the Baseline Day 1, Week 12, and End of Treatment visits and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-gp inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec.	12-lead ECG at Baseline Day 1, Week 12 and End of Treatment visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal LFTs are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal LFTs (AST or ALT > 3 x ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be checked at the beginning and end of the study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	Clinical chemistries assessing LFTs, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% across primary and secondary endpoint testing will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL.

Statistical analyses for all efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations. The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;

- Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method;
- Time to amenorrhea as measured by the by the alkaline hematin method;
- Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities;
- Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;
- Change from Baseline to Week 24 in uterine volume; and
- Change from Baseline to Week 24 in uterine fibroid volume.

The analysis methods used for the primary endpoint will be applied to the analyses of the secondary endpoints of proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment compared between relugolix Group B and placebo Group C, the proportion of patients with amenorrhea over the last 35 days, the proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of at least 1 g/dL at Week 24 and the proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume and time to amenorrhea, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions and stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, the Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline. The between treatment comparisons will be performed using model derived least squares means with treatment, stratification factors, baseline result accounted for in the model.

Baseline Numerical Rating Scale score is defined as the average Numerical Rating Scale score from the 35 days of data collected prior to the date of first dose of study drug after randomization. The Numerical Rating Scale score during the final study month is the average Numerical Rating Scale score during the last 35 days on treatment.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment group as treated. The treatment emergent period will be defined as the period of time from the first dose date of study drug through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE, version 5.0. All adverse events will be coded to preferred term and system organ class using MedDRA 12.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, v. 5.0 will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each parameter.

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. ECGs will also be read centrally. The distributions of corrected QT interval will be summarized at each visit. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), T-score for average of L1-L4, total hip, and femoral neck. All data will be listed and summarized by visit. The change, percent change from Baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

All data will be listed and summarized by visit. The change, percent change from baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by treatment arm.

The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5% or 6% by body area (lumbar, total hip, and femoral neck) will be estimated with 95% confidence intervals by treatment group. The number and percentage of patients meeting a T-score of < -2.5 by body area will also be estimated with 95% confidence interval by treatment group. Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.5. Pharmacokinetic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed:

- Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively;
- Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and

institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the IB, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the IB, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.

2) Patient clinical source documents. The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;
   - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
   - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
   - Concomitant medication (including start and end date); and
   - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publically Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

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APPENDICES

Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

Appendix 2. Daily eDiary

Clinical Study Medication

1. Did you take your dose of study treatment **today**?

   □ Yes

   If Yes, please provide

   Date: dd – MMM - yyyy

   Time: HH:MM [AM/PM]

   □ No

2. Did you take your dose of study treatment while **on an empty stomach**? (i.e., at least 1 hour before a meal)

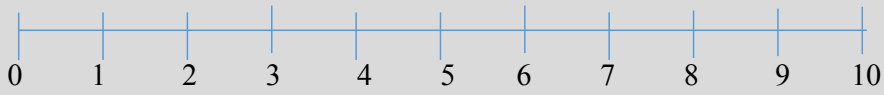
   □ Yes

   □ No

   □ Not applicable, I did not take a dose today

Uterine Fibroid Pain

Please rate your pain caused by your uterine fibroids by indicating the number that best describes your pain at its worst in the last 24 hours:



No Pain Pain As Bad As You Can Imagine

Menstrual Bleeding

1. Did you experience any menstrual bleeding **today**?

   □ Yes (this includes spotting as well as bleeding)

   □ No

2. Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?

   □ Yes

   □ No

Use of Pain Medication (Analgesics) and Supplements

1. Did you take any medication **today** to treat pain caused by your uterine fibroids?

   □ Yes

   If yes, record medication:_____

   □ No

Appendix 3. Menorrhgia Impact Questionnaire

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

	During the previous month, how distressed were you by...	Not at all	A little bit	Somewhat	A great deal	A very great deal
1	Heavy bleeding during your menstrual period	□	□	□	□	□
2	Passing blood clots during your menstrual period	□	□	□	□	□
3	Fluctuation in the duration of your menstrual period compared to your previous cycle	□	□	□	□	□
4	Fluctuation in the length of your monthly cycle compared to your previous cycle	□	□	□	□	□
5	Feeling tightness or pressure in your pelvic area	□	□	□	□	□
6	Frequent urination during the daytime hours	□	□	□	□	□
7	Frequent nighttime urination	□	□	□	□	□
8	Feeling fatigued	□	□	□	□	□

	During the previous month, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9	Made you feel anxious about the unpredictable onset or duration of your periods?	□	□	□	□	□
10	Made you anxious about traveling?	□	□	□	□	□
11	Interfered with your physical activities?	□	□	□	□	□
12	Caused you to feel tired or worn out?	□	□	□	□	□
13	Made you decrease the amount of time you spent on exercise or other physical activities?	□	□	□	□	□
14	Made you feel as if you are not in control of your life?	□	□	□	□	□
15	Made you concerned about soiling underclothes?	□	□	□	□	□
16	Made you feel less productive?	□	□	□	□	□
17	Caused you to feel drowsy or sleepy during the day?	□	□	□	□	□
18	Made you feel self-conscious of weight gain?	□	□	□	□	□
19	Made you feel that it was difficult to carry out your usual activities?	□	□	□	□	□
20	Interfered with your social activities?	□	□	□	□	□
21	Made you feel conscious about the size and appearance of your stomach?	□	□	□	□	□
22	Made you concerned about soiling bed linen?	□	□	□	□	□

	During the previous month, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23	Made you feel sad, discouraged, or hopeless?	□	□	□	□	□
24	Made you feel down hearted and blue?	□	□	□	□	□
25	Made you feel wiped out?	□	□	□	□	□
26	Caused you to be concerned or worried about your health?	□	□	□	□	□
27	Caused you to plan activities more carefully?	□	□	□	□	□
28	Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	□	□	□	□	□
29	Caused you embarrassment?	□	□	□	□	□
30	Made you feel uncertain about your future?	□	□	□	□	□
31	Made you feel irritable?	□	□	□	□	□
32	Made you concerned about soiling outer clothes?	□	□	□	□	□
33	Affected the size of clothing you wear during your periods?	□	□	□	□	□
34	Made you feel that you are not in control of your health?	□	□	□	□	□
35	Made you feel weak as if energy was drained from your body?	□	□	□	□	□
36	Diminished your sexual desire?	□	□	□	□	□
37	Caused you to avoid sexual relations?	□	□	□	□	□

Appendix 5. European Quality of Life Five-Dimension Five-Level Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

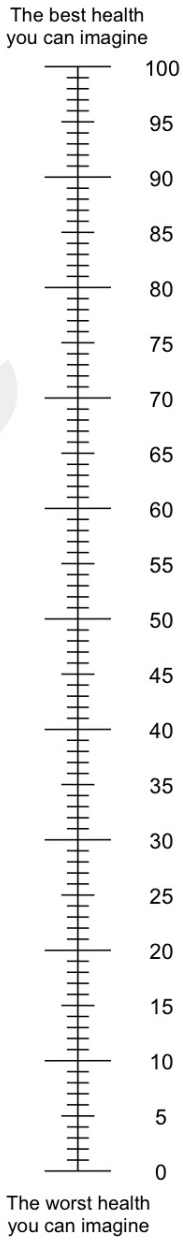
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6. Assessment of Abnormal Liver Function Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with low-dose estradiol and norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Appendix Table 1[a]; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • CBC with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.; • Serology for celiac disease; • Appropriate liver imaging; • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

16.1. Study Information

16.1.1. Protocol and Protocol Amendments

16.1.1.1. Original Protocol

16.1.1.2. Amendment 1

16.1.1.3. Amendment 2

CLINICAL STUDY PROTOCOL

Study Title:	An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
IND #:	131161
Version:	Original
Effective Date:	10-Nov-2016

SPONSOR SIGNATURE PAGE

An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3002

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

10 Nov 2016
Date

10 NOV 2016
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
EQ-5D	European Quality of Life Five-Dimension Five-Level
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menstrual Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart

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Term	Explanation
PD	pharmacodynamics
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
USP/NF	United States Pharmacopeia and the National Formulary
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3002
Location	Multinational, including North and South America, Europe, and Australia
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	<u>Primary Efficacy Objective</u> • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.
	<u>Secondary Efficacy Objectives</u> • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.

Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (~11 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal and/or transabdominal ultrasound. Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL each cycle for 2 cycles during the screening period. During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transabdominal and/or or transvaginal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will

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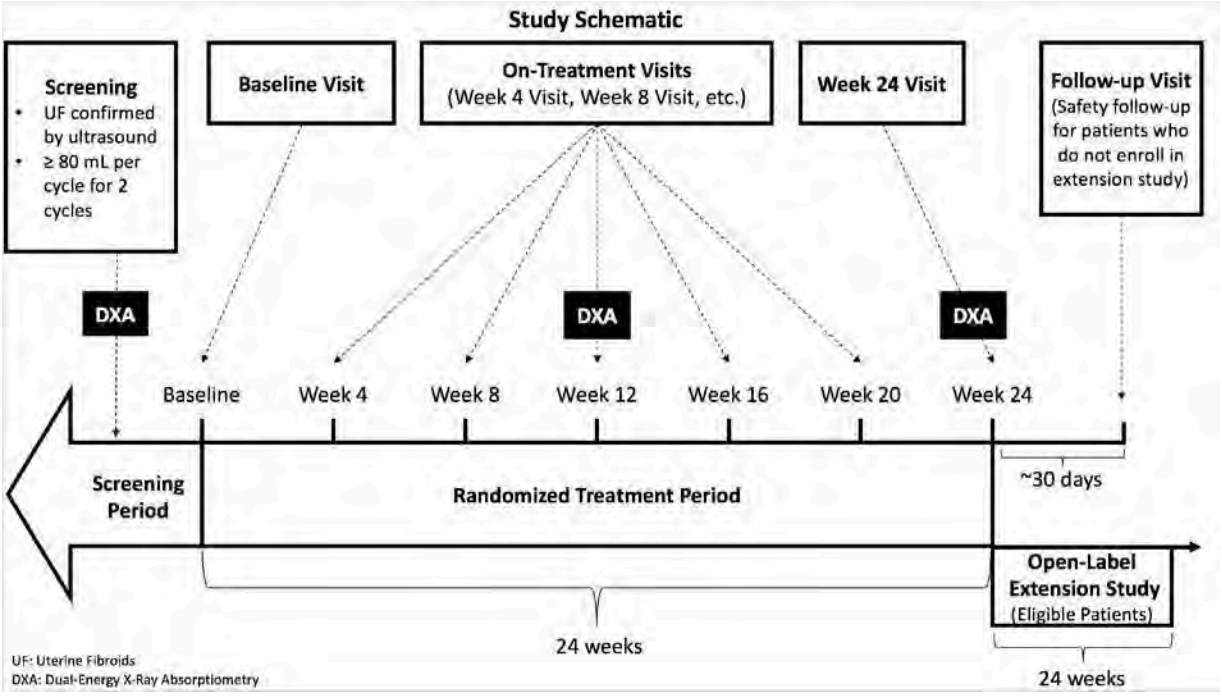
complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).



Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);
4. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
5. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal

ultrasound performed with saline or gel contrast during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
   a. Subserosal, intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter), or
   b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3;
6. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period;
7. Patient does not desire and is not expected to be a candidate for gynecological surgery or ablation procedures within the 6 months following enrollment;
8. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
9. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently during any required washout for excluded medications (if applicable), the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
10. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer);
11. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period;
12. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment;
2. Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine or total hip;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;

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7. Has a history of the use of bisphosphonates, calcitonin/calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Calculated creatinine clearance < 60 mL/min using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina;
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at

	any screening visit or the Baseline Day 1 visit; h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram; 15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit; 16. Has a history of clinically significant condition(s) including, but not limited to the following: a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded); b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma; c. History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year); 17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study; 18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable washout periods from these medications are also described therein); 19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form); 21. Has participated in a previous clinical study that included the use of relugolix; 22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling); 23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.
Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, color, and odor for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, color, and odor will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, color, and odor.

Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. <u>Primary Efficacy Endpoint</u> • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume. Safety Endpoints • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations (Cτ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.

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	Exploratory Endpoints • Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of 260 (130 patients in each of the relugolix and placebo arms) will provide $> 99\%$ power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be

presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE, version 5.0. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4),), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3002

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)	**Within 4 days after completion of menses**	**Within 4 days after completion of Screening 1 menses**	**Within 10 days of Screening 2 visit**	**Within 4 days after completion of 2nd Screening menses**	**Within 4 days of the start of menses**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X	X
Height	X												
Weight	X				X						X	X	X
Temperature	X				X						X	X	
Adverse Event Collection[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination, Including Visual Acuity[g]	X				X						X		
Gynecologic Examination with Pap Test, if applicable			X[h]								X		

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	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X	X
12-Lead Electrocardiogram			X		X			X			X	X	X
Clinical Laboratory Tests[l]	X	X			X[i, j]	X	X	X	X	X	X[i, k]	X[l]	X
PK Sample[m]					X	X		X			X	X[l]	
PD Sample[n] and Administer Dose of Study Drug in Clinic	X				X	X	X	X	X	X	X		X
PGx Sample[o]					X								
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X		
Urinalysis	X				X								
Mammogram[p]			X										
Transvaginal or Transabdominal Ultrasound[q]			X								X		
Endometrial Biopsy[r]			X								X[s]		
Bone Densitometry[t]			X					X			X		
Randomization[u]					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X			
Dispense Study Treatment					X	X	X	X	X	X			
Patient eDiary[v]			X	X	X	X	X	X	X	X	X		
Feminine Product Collection and Venous Blood Sample[w]		X		X		X	X	X	X	X	X		
MIQ					X	X	X	X	X	X	X		
UFS-QoL					X			X			X		
EQ-5D					X						X		
Treatment Compliance						X	X	X	X	X	X	X	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Status of Menstruation Recovery													X

Abbreviations: EQ-5D, European Quality of Life Five-Dimension Five-Level Scale; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; UFS-QoL, Uterine Fibroid Score – Quality of Life

a. The screening period should be initiated after the informed consent form is signed and any required washout for excluded medications or devices is complete.
b. Visit to occur within 4 days of the completion of menses.
c. Visit to occur within 10 days after Screening 2 visit if the menstrual blood loss is determined to be ≥ 80 mL. The Screening 1 or Screening 2 visits for alkaline hematin menstrual blood loss may be repeated at the discretion of the investigator if one menstrual cycle does not meet MBL criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 4 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose PD sample, pregnancy and urinalysis test samples prior to first dose of study drug. The patient must complete MIQ, UFS-QoL, and EQ-5D questionnaires prior to first dose of study drug.
e. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003), a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~4 weeks after an Early Termination visit).
f. Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.
g. Complete Physical Exam (not including a gynecological examination). Visual acuity must be assessed with a standard eye chart. The patient should wear any prescription glasses or contacts during the assessment.
h. Papanicolaou test must be conducted for women without a test result 6 months prior to the Screening 1 visit. Re-measurement should be performed for inadequate or false-positive results.
i. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state for the Baseline and Week 24 visit clinical laboratory tests.
j. At the Baseline Day 1 visit (clinical laboratory tests in fasted state), in addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, iron, ferritin, and hemoglobin A1c. An additional sample will be collected at this visit and stored for possible future testing for presence of hepatitis A, B, and C if required per request from medical monitor to assess etiology of liver test abnormalities.

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k. At the Week 24 visit or Early Termination visit (clinical laboratory tests in fasted state), in addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.
l. For an Unscheduled visit, a central safety laboratory assessment or PK sample collection is performed as needed.
m. Pharmacokinetics samples: Samples should be obtained in the fasted since study drug is administered on an empty stomach. Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics sample collections are complete (with the exception of Week 24 when no dose is administered).
n. Pharmacodynamic samples: Samples should be obtained in the fasted since study drug is administered on an empty stomach, collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Instruct the patient not to take her study treatment at home on these visit days. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Screening 1 visit, Week 24 and Follow Up visits when no dose is administered).
o. Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive).
p. Patients ≥ 39 years of age at the time of the Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period; if not, schedule at the Screening 3 visit.
q. Transvaginal or transabdominal ultrasound with saline or gel contrast must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps. Results must be submitted to and confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is the preferred procedure. A transabdominal ultrasound may also be obtained if indicated, for example, by extension of large masses outside the pelvis.
r. Endometrial biopsy is performed at Screening after the first acceptable alkaline hematin sample collection.
s. Endometrial biopsy is to be performed at the Week 24 visit if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized) and may be requested for central review if abnormal.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results available prior to randomization.
u. Randomization: After a patient is screened and the investigator determines that the patient is eligible for randomization the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the Study Reference Manual. The sponsor (or designee) will approve the patient's randomization in writing. Once the site has received approval, the patient may undergo her Baseline Day 1 visit.
v. Patient electronic diary: Patients enter diary information on a daily basis for their compliance with (study treatment starting at Baseline/Day 1), menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening visit 2 and compliance with study treatment starting at Baseline/Day 1 through Week 24 or early termination.
w. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.

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2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which are

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administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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Relugolix antagonizes the human GnRH receptors present on the gonadotrophin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 µg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 µg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 µg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥100 mg/kg (estimated C_{max} of 4.0 µg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 µg/mL).

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2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and three phase 2 studies (including one in women with uterine fibroids and two in women with endometriosis) have been completed. In addition, six clinical studies evaluating relugolix are ongoing, including two phase 1 studies, two phase 2 studies in men with prostate cancer (US and Europe), and two phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least one dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

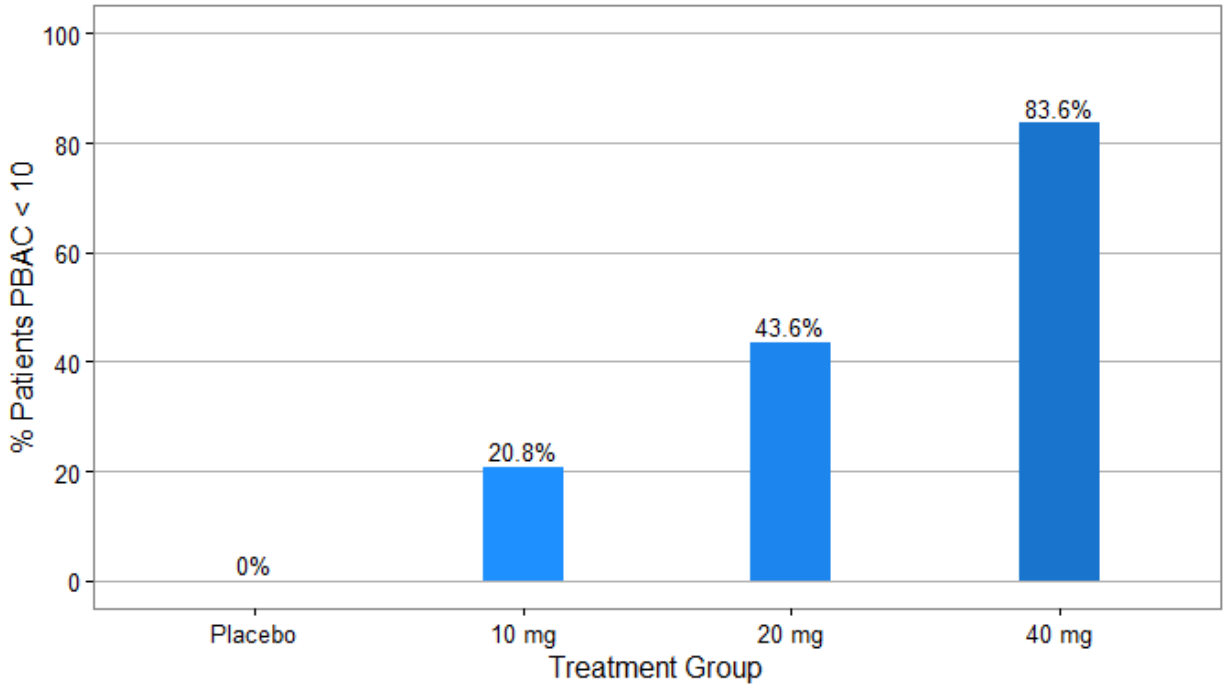
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 45%. The exposure of relugolix is increased by inhibitors of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of

cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver function test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

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Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 interim analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤50 ng/dL) and maintained these levels through at least 24 weeks. These data are comparable to testosterone levels achieved by leuprolide 22.5 mg every 3 months. Study C27003 demonstrated rapid and sustained suppression of testosterone levels for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, Version 9.0, dated 09 November 2016, along with a full discussion of the safety profile of relugolix.

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3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
Primary Efficacy	
• To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by

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Objective(s)	Endpoint(s)
	the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks.	• Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.
<u>Pharmacokinetic and Pharmacodynamic</u>	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-

Objective(s)	Endpoint(s)
low-dose estradiol and norethindrone acetate.	dose concentrations of LH, FSH, estradiol, and progesterone.
Exploratory	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or the placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (~11 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by a centrally-reviewed transvaginal and/or transabdominal ultrasound. Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for each of 2 cycles during the screening period. During the randomized treatment period, study participants will take blinded study drug orally once daily for 24 weeks. Women with iron-deficient microcytic anemia with a hemoglobin ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A

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transabdominal and/or or transvaginal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized). Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Samples will also be collected for PK assessment of relugolix, estradiol, and norethindrone, and for the pharmacodynamic assessment of LH, FSH, estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit to assess safety approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits and dispensation and collection of feminine products during this time are provided in Figure 4-2.

Figure 4-1 MVT-601-3002 Study Schematic

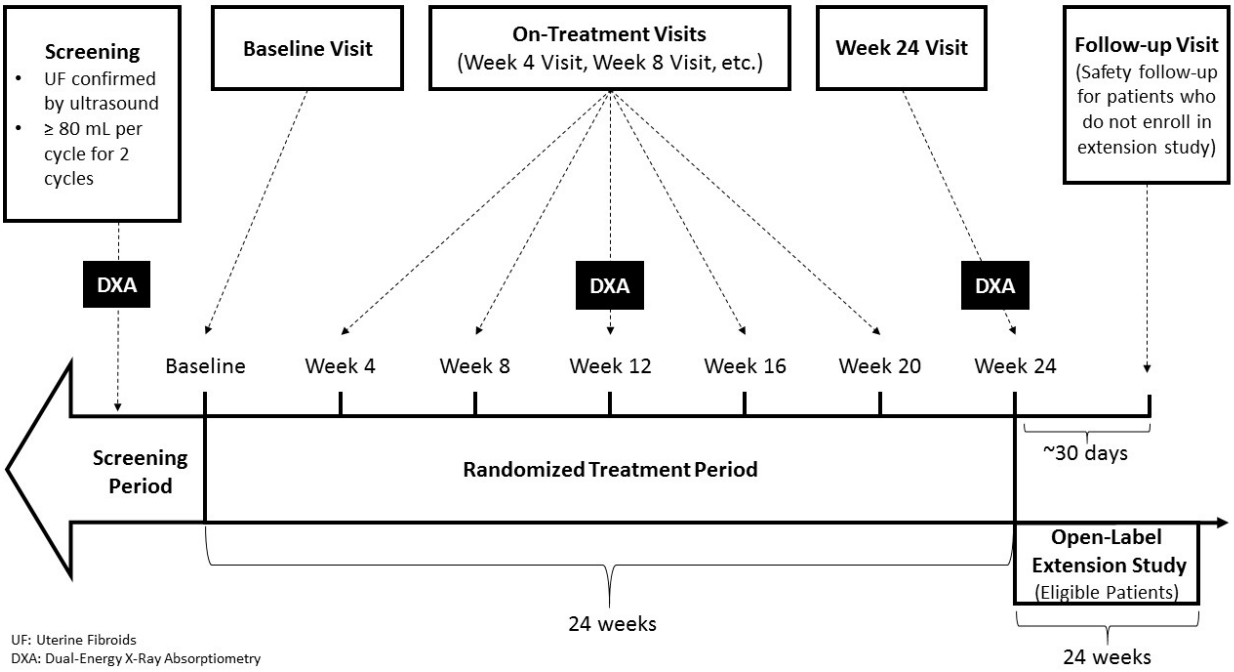
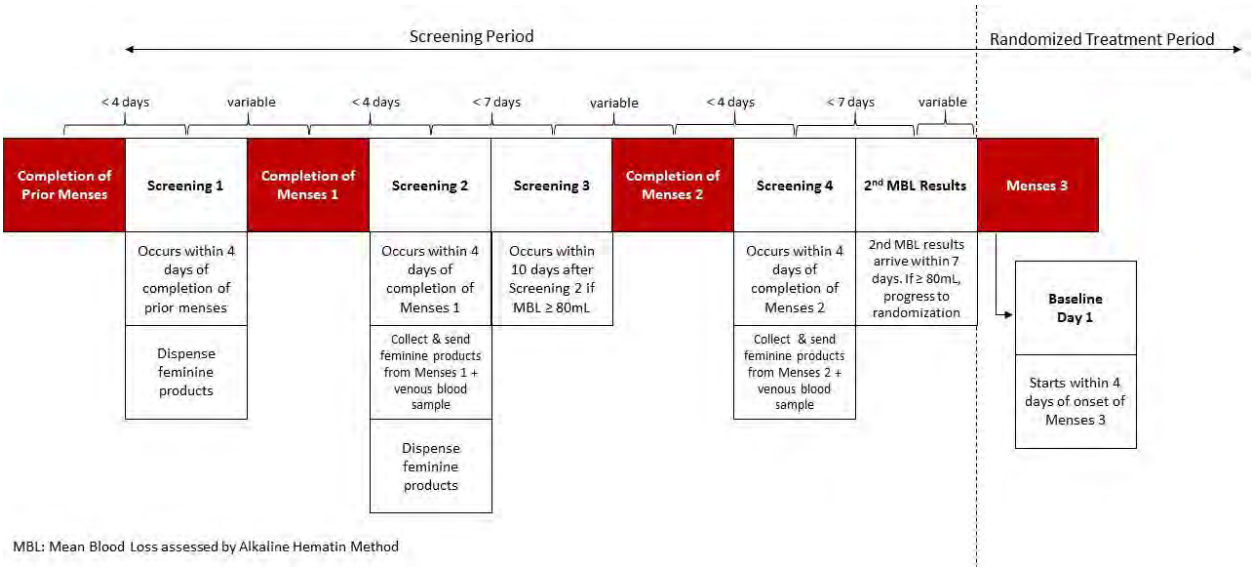


Figure 4-2 Schematic of MVT-601-3002 Screening Visits and Feminine Product Dispensation and Collection during the Screening Period



4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This study will focus on the primary objective of demonstrating a reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study is designed to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An extension study is planned to provide additional safety and efficacy data through 48 weeks.

Women with uterine fibroids and heavy menstrual blood loss by the alkaline hematin method of ≥ 80 mL/cycle as assessed during two cycles will be enrolled in this study. Randomization will be 1:1:1. Placebo was selected as the appropriate control for the study because there is no standard of care medical therapy for the long-term treatment of women with uterine fibroids and heavy menstrual bleeding. Commonly-used treatment options range from combined oral contraceptive pills, which are not effective in many cases, levonorgestrel-containing intrauterine devices, and leuprolide therapy indicated for 3 months in the preoperative setting.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. This dose was selected for evaluation in phase 2 clinical studies based upon phase 1 data demonstrating similar estradiol and progesterone suppression in women treated with single doses of relugolix 40 mg or 80 mg, and data demonstrating that premenopausal women treated with multiple doses of 40 mg once daily relugolix over 14 days had estradiol levels suppressed to a median value of 3.68 pg/mL.

Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, as described above, a phase 2 study of doses of relugolix 10, 20 and 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 48 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 48 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 1992; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the US as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate has demonstrated that this dose of add-back therapy maintains serum estradiol in the 25-50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the

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addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet; Activella US Prescribing Information, 2013) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy and is not included as a control arm as it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study will primarily assess the efficacy and safety of relugolix 40 mg co-administered with a low-dose of estradiol and norethindrone acetate compared with placebo at 24 weeks to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes. An additional arm with monotherapy relugolix administered for 12 weeks followed by 12 weeks of relugolix co-administered with low-dose hormonal add-back therapy is included to provide data on the requirement for hormonal therapy to mitigate the adverse relugolix side effects of bone mineral density loss and hot flushes.

All eligible women who complete the 24-week study will be offered the opportunity to enroll in an open-label extension study to obtain long-term safety and efficacy data over an additional 24 weeks of treatment, providing approximately 1 year of safety data on the women originally randomized to relugolix.

4.3. Selection of Study Population

The study population will include approximately 390 premenopausal women aged 18 to 50 years with heavy menstrual bleeding (≥ 80 mL over 2 cycles by the alkaline hematin method) associated with uterine fibroids demonstrated over two cycles during the screening period.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for randomization and enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Baseline Day 1 visit, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);
4. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
5. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal ultrasound performed with saline or gel contrast during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3;
6. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period;
7. Patient does not desire and is not expected to be a candidate for gynecological surgery or ablation procedures within the 6 months following enrollment;
8. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
9. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently during any required washout for excluded medications (if applicable), the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
10. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer);
11. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period;

12. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment;
2. Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine or total hip;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin/calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);

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12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Calculated creatinine clearance < 60 mL/min using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina;
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year);

17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable washout periods from these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

4.5. Method of Assigning Patients to Treatment Group and Patient ID Number

After a patient is screened and the investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the Study Reference Manual. The sponsor (or designee) will approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient's Baseline Day 1visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient Identification Number.

4.6. Removal of Patients from Therapy

Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

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The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Patients who have percent change from Baseline in bone mineral density at either the Week 12 or Week 24 visit (or any unscheduled visit) at the lumbar spine (average L1-L4), total hip, or femoral neck of < -4.0 that is repeated and confirmed (ie, both values are < -4.0);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.6 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of dual contraception are:

- Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 1 month following the last study visit.

A patient may start hormonal contraception 4 weeks after her last study visit provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including just prior to receiving first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

Each patient will be instructed to take one tablet and one capsule per day.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, color, and odor. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

Table 5-1 Description of MVT-601-3002 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An over-encapsulated round film-coated white tablet with placebo back-fill material	Capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 12 or 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™).

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the United States Pharmacopeia and the National Formulary (USP/NF) excipients.

Placebo to match relugolix is a pink tablet using USP/NF excipients.

The fixed-dose combination tablet of estradiol 1.0 mg and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient USP/NF grade back-fill material.

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3002 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with relugolix placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

Patients should take any oral iron supplementation with meals.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK/PD samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event.

Patients may subsequently be re-started on study drug, with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 1°C to 30°C until it is used or returned to the sponsor (or designee). A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix, the estradiol/norethindrone acetate combination, relugolix placebo, and the estradiol/norethindrone acetate placebo to be distributed will meet all applicable requirements of the US FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Relugolix 40 mg and relugolix placebo will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate or estradiol/norethindrone acetate placebo.

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient's individual study treatment, however, the Investigator should make every effort to first contact the medical monitor or appropriate study personnel to discuss options **before** unblinding the patient's treatment assignment. If unblinding occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient, unless that information is important for the safety of patients currently in the study. Patients whose treatment assignment has been unblinded will be permanently discontinued from treatment.

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The sponsor (or designee) **may** unblind the treatment assignment for any patient with a serious adverse event.

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and prior to each visit, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused stud drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

This table provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Washout Periods

Drug Class	Examples	Washout Period/Comments
Bisphosphonates	alendronate etidronate	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	1 month
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone	2 months (6 months for depot subcutaneous or intramusclar injections)

Drug Class	Examples	Washout Period/Comments
Estrogens	estradiol valerate conjugated estrogens	2 months (6 months for depot subcutaneous or intramusclar injections)
Oral Contraceptives	combined or progestin only	2 months
Selective Estrogen Receptor Modulators	raloxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	2 months
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin, calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	2 months
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin tranexamic acid vitamin k preparations	1 month
Glucocorticoids	prednisolone or prednisone dexamethasone	No washout Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction Short duration ($\leq$ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	carbamazepine rifampin St John's wort	2 weeks

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Drug Class	Examples	Washout Period/Comments
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporin diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole lopinavir/ritonavir quercetin quinidine ranolazine ticagrelort verapamil	2 weeks (6 months for amiodarone)

Abbreviation: GnRH, gonadotropin-releasing hormone

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

Use of analgesics is **ONLY permitted under the following conditions** from the Screening 1 visit to the Week 24 (or Early Termination) visit:

- Ibuprofen or other non-steroidal anti-inflammatory medications can be used as the first choice medicine for pain **associated with uterine fibroids**. Narcotic analgesics should be used for severe pain that cannot otherwise be controlled.
- Acetaminophen can be used as the first choice medicine for treatment of an adverse event or other pain **NOT associated with uterine fibroids** such as headache or a common cold.
- Analgesics for topical/external use are also permitted.
- Codeine that is not intended to relieve pain associated with uterine fibroids (eg, codeine phosphate in a combination cold remedy) is permitted.

This restriction was set because analgesic medications are likely to have an impact on the evaluation of a secondary endpoint regarding pain. Analgesics refer to drugs containing compounds that have indications for pain symptoms in the package inserts and antispasmodic drugs that possess indications for gynecological or urological disease in the package inserts.

Patients should be instructed not to use analgesics for prophylactic purposes. Patients should also be instructed to record in the eDiary their worst pain symptoms during the past 24 hours before taking analgesics.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL but ≤ 10 g/dL, a mean corpuscular volume below normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.7. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities in the study synopsis (see Section 1.1). The study is divided into three periods: screening period, randomized treatment period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study; unscheduled visits may also occur as needed to evaluate patients).

6.2. Screening Period

Pre-screening evaluation, not including any study procedures or tests, may be conducted prior to the initial formal screening evaluation at the Screening 1 visit in an effort to identify patients unlikely to meet study-related entry criteria. Review of medical history, menstrual history, and prior uterine imaging assessments is permitted. Patients should have a diagnosis of uterine fibroids and a history of heavy menstrual bleeding with or without associated pain on a background of generally regular menses (ie, regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next cycle) as reported by the patient for at least 3 months prior to the Screening 1 visit.

The screening period consists of the Screening 1, 2, 3, and 4 visits. See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening.

The Screening 1 visit will be conducted following the signing of the informed consent form and should occur within 4 days after completion of menses. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications and SAEs, obtaining of clinical evaluations including vital signs, height, weight, temperature, a complete physical examination including visual acuity (not including a gynecological examination), clinical laboratory tests, urinalysis, and a urine pregnancy test will be conducted. Feminine product will be dispensed with instructions to collect and return all product used during the next menses.

Screening 2 visit is scheduled to occur within 4 days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine product to determine if their menstrual blood loss is ≥ 80 mL. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine product will be dispensed for collection of menstrual blood loss during the next menses.

The patient will return for the Screening 3 visit within 10 days of Screening 2 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL. At the Screening 3 visit 3, review of inclusion and exclusion criteria will be conducted confirmation of continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. In addition, the patient will undergo a gynecological examination (a Papanicolaou test must be conducted for women without a test result 6 months prior to the Screening 1 visit). Re-measurement should be performed for inadequate or false-positive results. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. A transvaginal and/or transabdominal pelvic ultrasound with saline or gel contrast will be performed to assess for uterine fibroids. The anatomic location and size of the fibroid disease will be estimated. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to randomization). An endometrial biopsy will be obtained. Bone densitometry by DXA of the lumbar spine, total hip, and femoral neck will be scheduled to be completed prior to randomization for submission to central reader. Patients who will be ≥ 39 years of age at the time of the Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) within 3 months prior to the Screening 1 visit. If not, a mammogram will also be scheduled as a part of Screening 3 visit.

Patients will be provided with the eDiary instructions at this Screening 3 visit and will be dispensed feminine products to be gathered for the second cycle. Each patient will begin recording information into the eDiary including menstrual bleeding and use of feminine products for menstrual bleeding (ie, on the day of Screening 3 visit). The eDiary will be maintained on a daily basis for the duration of the study up until the day before the Week 24 (or Early Termination) visit.

The Screening 4 visit is scheduled to occur within 4 days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn

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for hemoglobin assessment. The patient's eDiary data collection will be reviewed. Laboratory and imaging evaluations will be reviewed to ensure eligibility for randomization.

At the discretion of the investigator, the Screening 1 or 2 visits can be repeated if one menstrual cycle does not meet the heavy menstrual bleeding alkaline hematin criteria and it is thought to be due to an inadequate collection by a highly motivated patient. A Randomization Authorization Form must be submitted to the sponsor for approval prior to conducting the Baseline Day 1 visit. The Baseline Day 1 visit should be scheduled to coincide as closely as possible to when the patient will be finished with her next menses.

6.3. Randomized Treatment Period (Baseline to Week 24)

At the Baseline Day 1 visit, patients will be randomized to one of the three study treatment arms (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the Week 24 visit. Patients will continue recording daily in their eDiary. On-treatment study visits will occur every 4 weeks through the end of Week 24. At each post-baseline visit, patients will return their feminine products for alkaline hematin testing. Safety monitoring including signs and symptoms directed physical examination, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12 and 24 visits. A repeat transabdominal and/or transabdominal ultrasound and endometrial biopsy will be performed at the Week 24 visit. The endometrial biopsy will be read locally. Study drug and eDiary compliance will be reviewed at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the randomized treatment period.

Sites should try to schedule patient visits during the morning, instructing patients to arrive before taking their study drug to allow for pre-dose PK/PD sampling. Patients should come to the clinic in the fasted state (eg, nothing to eat or drink after midnight the day before the clinic visit).

6.4. Continuation into Extension Study

It is expected that most patients will enter the 24-week extension study (MVT-601-3003), which will be conducted under a separate protocol. Patients will provide separate informed consent to participate in the extension study during which all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate.

6.5. Follow-up Visit

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3003), will have a Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation. Patients who withdraw early from this study will also undergo the Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Refer to

the Schedule of Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits conducted to evaluate adverse events: vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment and PK sample if indicated, 12-lead ECG, recording of concomitant medications, and study drug compliance.

6.7. Study Procedures

6.7.1. Efficacy-Related Procedures

6.7.1.1. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.7.1.2. Transvaginal and/or Transabdominal Ultrasound

Transvaginal and/or transabdominal ultrasound with saline or gel contrast is performed for the diagnosis of uterine fibroids, to determine uterine and myoma volumes, and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single physician (investigator or sub-investigator) will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Transvaginal ultrasound is preferred, but transabdominal ultrasound may be used as necessary for full visualization of the uterus. The ultrasound method used at screening should be repeated for the ultrasound at the Week 24 visit.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = D1 x D2 x D3 x π / 6
Where:
D1 = the longest diameter of the myoma or uterus (unit of length: cm)
D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

6.7.1.3. Endometrial Biopsy

An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A second biopsy is to be performed at the Week 24 if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized). The biopsies will be read locally, but biopsies may be requested for central review.

6.7.1.4. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.7.1.5). To maintain blinding, concentrations of these hormones should be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.7.1.5. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping procedures

are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.7.1.6. Patient eDiary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. During menstruation, patients will complete daily diaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will act as its own source data and these data will be reviewed by the investigator to identify any potential adverse events.

6.7.1.7. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 3). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the randomized treatment period. Patients will complete the MIQ at each visit at the site before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.8. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom – Quality of Life (UFS-QoL) score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). Patients will complete the UFS-QoL questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.9. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale (EQ-5D) is a standardized instrument for use as a measure of health outcomes (see Appendix 5). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued,

6.7.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one 5-mL sample of whole blood will be collected and stored for future pharmacogenomic analyses. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.7.2. Safety-Related Procedures

6.7.2.1. Weight, Height, and Body Mass Index

Patients should have weight and height measured while wearing indoor clothing and with shoes removed.

6.7.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.7.2.3. Physical and Gynecologic Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. Visual acuity will be checked at the beginning and end of the study by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for women without an available test result from within 6 months prior to the Screening 1 visit. Re-measurement should be performed for inadequate or false-positive results.

6.7.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium	White Blood Cell (WBC) Count	Qualitative
Chloride	WBC Differential	Protein
Bicarbonate	Red Blood Cell Count	Glucose
Blood Urea Nitrogen	Hemoglobin	Occult blood
Creatinine	Hematocrit	Urobilinogen
Glucose	Mean Corpuscular Volume	Bilirubin
Calcium	Platelet Count	Pregnancy test
Phosphate		(human chorionic gonadotropin)
Magnesium		
Albumin		
Total Protein		
Alkaline Phosphatase		
Lactate Dehydrogenase		
Creatine Kinase		
Liver Function Tests including:		
Bilirubin Total		
Alanine Aminotransferase		
Aspartate Aminotransferase		
Gamma-Glutamyl Transferase		
Lipid Profile including:		
Total Cholesterol		
Low Density Lipoprotein		
High Density Lipoprotein		
Triglycerides		

Specialized Hormonal Assessments: Thyroid-Stimulating Hormone Parathyroid Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Iron (Baseline only) Ferritin ((Baseline only) Hemoglobin A1c (Baseline and Week 24 only)		

A separate sample will be collected at the Day 1 visit and will be banked and tested for presence of hepatitis A, B, and C (hepatitis A antibody, IgM, hepatitis B core antibody, IgM, hepatitis B surface antigen, and hepatitis C antibody) if requested by the medical monitor for evaluation of abnormal liver function tests.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory or laboratories used.

6.7.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.7.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient).

The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.

6.8. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of 5 mL of whole blood collected for pharmacogenomics testing (see Section 6.7.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), ECGs, bone mineral density assessments, endometrial biopsy results, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;

- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are 'intermittent'. All other events are 'continuous'. Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted, however, study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events which jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local Institutional Review Board (IRB) or Institutional Ethics Committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's eDiary entries and answers to the UFS-QoL will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents.
In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient or partner will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1).

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit approximately 30 days after the last dose of study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Any event occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE, version 5.0. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE Version 5.0

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized treatment period or the Follow-up visit should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet SAE criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the International Normalized Ratio (INR) >1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
   - Alcoholic hepatitis
   - Nonalcoholic steatohepatitis
   - Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

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7.6. Serious Adverse Event Reporting

Using a serious adverse event report form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.

The contact information for submission of serious adverse events and events of overdose or pregnancy is available on the Serious Adverse Event report form. Information may also be provided to PPD

The initial report should include:

- Study number (MVT-601-3002)
- Site name and number
- Investigator name
- Patient ID number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity)
- Causal relationship to the study drug

If the patient died, the report should include the cause of death and whether or not the cause of death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (ie, more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;

- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy reporting forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.7.2 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, electrocardiograms and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine fibroids. Low-dose hormonal add-back therapy with estradiol and norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (QTc

prolongation), hepatic enzyme increases, PLD, reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, osteopenia, metabolic bone disease, and prior medical therapy for low bone mineral density.	Bone mineral density will be monitored at the Baseline Day 1, Week 12, and End of Treatment visits and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-gp inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec.	12-lead ECG at Baseline Day 1, Week 12 and End of Treatment visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal LFTs are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal LFTs (AST or ALT > 3 x ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be checked at the beginning and end of the study.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	Clinical chemistries assessing LFTs, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% across primary and secondary endpoint testing will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

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9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥225 mL.

Statistical analyses for all efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations. The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;
- Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method;
- Time to amenorrhea as measured by the by the alkaline hematin method;
- Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities;

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- Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;
- Change from Baseline to Week 24 in uterine volume; and
- Change from Baseline to Week 24 in uterine fibroid volume.

The analysis methods used for the primary endpoint will be applied to the analyses of the secondary endpoints of proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment compared between relugolix Group B and placebo Group C, the proportion of patients with amenorrhea over the last 35 days, the proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of at least 1 g/dL at Week 24 and the proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume and time to amenorrhea, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions and stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, the Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline. The between treatment comparisons will be performed using model derived least squares means with treatment, stratification factors, baseline result accounted for in the model.

Baseline Numerical Rating Scale score is defined as the average Numerical Rating Scale score from the 35 days of data collected prior to the date of first dose of study drug after randomization. The Numerical Rating Scale score during the final study month is the average Numerical Rating Scale score during the last 35 days on treatment.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment group as treated. The treatment emergent period will be defined as the period of time from the first dose date of study drug through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

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The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE, version 5.0. All adverse events will be coded to preferred term and system organ class using MedDRA 12.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, v. 5.0 will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each parameter.

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. ECGs will also be read centrally. The distributions of corrected QT interval will be summarized at each visit. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), T-score for average of L1-L4, total hip, and femoral neck. All data will be listed and summarized by visit. The change, percent change from Baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

All data will be listed and summarized by visit. The change, percent change from baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by treatment arm.

The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5% or 6% by body area (lumbar, total hip, and femoral neck) will be estimated with 95% confidence intervals by treatment group. The number and percentage of patients meeting a T-score of < -2.5 by body area will also be estimated with 95% confidence interval by treatment group. Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.5. Pharmacokinetic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed:

- Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively;
- Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the IB, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to

prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the IB, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
    - Patient identification (name, date of birth, gender);
    - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
    - Participation in the study (including study number);
    - Study discussed and date of informed consent;
    - Dates of all visits;
    - Documentation that protocol-specific procedures were performed;
    - Results of efficacy parameters, as required by the protocol;
    - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
    - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
    - Concomitant medication (including start and end date); and
    - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and

until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor,

the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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10.2.3. Posting of Information on Publically Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

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The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

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APPENDICES

Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

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Appendix 2. Daily eDiary

Clinical Study Medication

1. Did you take your dose of study treatment **today**?

   □ Yes

   If Yes, please provide

   Date: dd – MMM - yyyy

   Time: HH:MM [AM/PM]

   □ No

2. Did you take your dose of study treatment while **on an empty stomach**? (i.e., at least 1 hour before a meal)

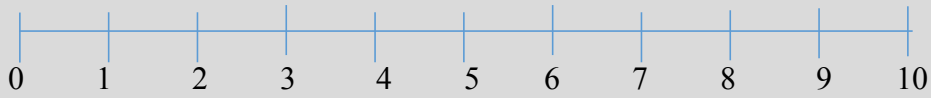
   □ Yes

   □ No

   □ Not applicable, I did not take a dose today

Uterine Fibroid Pain

Please rate your pain caused by your uterine fibroids by indicating the number that best describes your pain at its worst in the last 24 hours:



No Pain Pain As Bad As You Can Imagine

Menstrual Bleeding

1. Did you experience any menstrual bleeding **today**?

   □ Yes (this includes spotting as well as bleeding)

   □ No

2. Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?

   □ Yes

   □ No

Use of Pain Medication (Analgesics) and Supplements

1. Did you take any medication **today** to treat pain caused by your uterine fibroids?

   □ Yes

   If yes, record medication:_____

   □ No

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Appendix 3. Menorrhgia Impact Questionnaire

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

	During the previous month, how distressed were you by...	Not at all	A little bit	Somewhat	A great deal	A very great deal
1	Heavy bleeding during your menstrual period	□	□	□	□	□
2	Passing blood clots during your menstrual period	□	□	□	□	□
3	Fluctuation in the duration of your menstrual period compared to your previous cycle	□	□	□	□	□
4	Fluctuation in the length of your monthly cycle compared to your previous cycle	□	□	□	□	□
5	Feeling tightness or pressure in your pelvic area	□	□	□	□	□
6	Frequent urination during the daytime hours	□	□	□	□	□
7	Frequent nighttime urination	□	□	□	□	□
8	Feeling fatigued	□	□	□	□	□

	During the previous month, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9	Made you feel anxious about the unpredictable onset or duration of your periods?	□	□	□	□	□
10	Made you anxious about traveling?	□	□	□	□	□
11	Interfered with your physical activities?	□	□	□	□	□
12	Caused you to feel tired or worn out?	□	□	□	□	□
13	Made you decrease the amount of time you spent on exercise or other physical activities?	□	□	□	□	□
14	Made you feel as if you are not in control of your life?	□	□	□	□	□
15	Made you concerned about soiling underclothes?	□	□	□	□	□
16	Made you feel less productive?	□	□	□	□	□
17	Caused you to feel drowsy or sleepy during the day?	□	□	□	□	□
18	Made you feel self-conscious of weight gain?	□	□	□	□	□
19	Made you feel that it was difficult to carry out your usual activities?	□	□	□	□	□
20	Interfered with your social activities?	□	□	□	□	□
21	Made you feel conscious about the size and appearance of your stomach?	□	□	□	□	□
22	Made you concerned about soiling bed linen?	□	□	□	□	□

	During the previous month, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23	Made you feel sad, discouraged, or hopeless?	□	□	□	□	□
24	Made you feel down hearted and blue?	□	□	□	□	□
25	Made you feel wiped out?	□	□	□	□	□
26	Caused you to be concerned or worried about your health?	□	□	□	□	□
27	Caused you to plan activities more carefully?	□	□	□	□	□
28	Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	□	□	□	□	□
29	Caused you embarrassment?	□	□	□	□	□
30	Made you feel uncertain about your future?	□	□	□	□	□
31	Made you feel irritable?	□	□	□	□	□
32	Made you concerned about soiling outer clothes?	□	□	□	□	□
33	Affected the size of clothing you wear during your periods?	□	□	□	□	□
34	Made you feel that you are not in control of your health?	□	□	□	□	□
35	Made you feel weak as if energy was drained from your body?	□	□	□	□	□
36	Diminished your sexual desire?	□	□	□	□	□
37	Caused you to avoid sexual relations?	□	□	□	□	□

Appendix 5. European Quality of Life Five-Dimension Five-Level Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

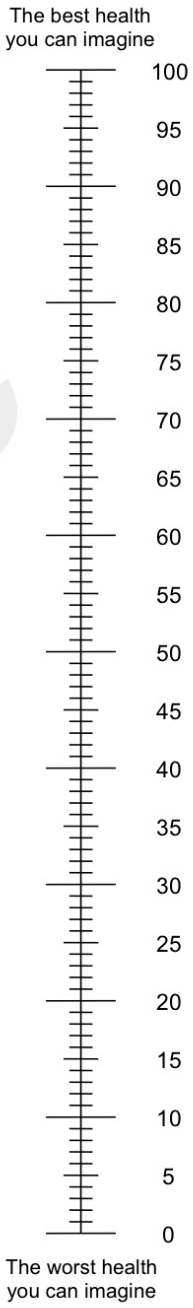
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6. Assessment of Abnormal Liver Function Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with low-dose estradiol and norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents;
- Prior and concurrent use of alcohol, recreational drugs, and special diets;
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms;
- Physical examination.

Recommended tests:

Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist.

- Repeat liver tests as per Appendix Table 1[a];
- Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests;
- CBC with differential to assess for eosinophilia;
- Serum acetaminophen (paracetamol) concentration;
- Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus;
- Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.;
- Serology for celiac disease;
- Appropriate liver imaging;
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

AMENDMENT 2: SUMMARY OF CHANGES

Protocol MVT-601-3002 entitled "LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids" has been amended as described in the table below. The main purpose of the amendment was to provide clarification regarding roll-over of patients into the extension study MVT-601-3003 and follow-up assessments for patients who do not enroll in the extension study. Modifications were also made to the secondary efficacy endpoints related to disease related symptoms and impact of disease on activities, function and quality of life. This includes the addition of a new patient global assessments for function and symptoms. The amendment also includes modifications or clarifications to study eligibility as well as study procedures or tests. A detailed list of changes is described below. Note that corrections of typos, minor clarifications and minor wording changes to improve readability and understanding are not included in this table.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Synopsis: Location	Multinational, including North and South America, Europe, and Australia	Multinational, including North and South America, **South Africa, and** Europe ~~**and Australia**~~	To update regions where study is conducted.
Title Page: Sponsor	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland	Myovant Sciences GmbH **Viaduktstrasse 8** **4051** Basel Switzerland	Sponsor address updated.
Synopsis: Secondary Efficacy Objectives Section 3 Study Objective and Endpoints	• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: … None. None.	• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: … o Impact of uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient	To add a new secondary efficacy objective related to the impact of uterine fibroids on symptoms, activities, and QOL and to add a patient global assessment for function and symptoms. Clarified the instrument to be used for assessing impact of heavy menstrual bleeding on social, leisure and physical activities.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		Global Assessment (PGA) for function and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities **as measured by the Menorrhagia Impact Questionnaire (MIQ)**; o **Pain associated with uterine fibroids;**	
	o Impact of heavy menstrual bleeding on social, leisure, and physical activities;		
Synopsis: Safety Objectives Section 3 Study Objective and Endpoints	None. None.	• To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids.	Objectives related to BMD analysis at 12 weeks and analysis of vasomotor symptoms are added
Synopsis: Study Design Section 4.1 Overall Study Design Section 5.1 Treatments Administered	During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks.	During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. **The last dose of study drug for the Randomized Treatment Period will be taken on the immediate day prior to the Week 24 visit.**	To allow transition into the extension study (MVT-601-3003). Week 24 visit will be the first day of MVT-601-3003. Patients who qualify for and provide informed consent to enroll in MVT-601-3003 will take the first dose of open label study drug at Week 24.
Synopsis: Study Design	All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and	During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken	Added additional text to provide details on the transition of patients into the extension study (MVT601-3003). The Week 24 visit will be the

Item; Section(s)	Amendment 1	Amendment 2	Rationale
	norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit to assess safety approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).	on the day immediately before to the Week 24 visit. Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).	first day of the extension study. Also added additional follow-up activities for patients not enrolling into the extension study.
Synopsis: Inclusion Criteria Section 4.3.1 Inclusion Criteria Section 4.7 Contraception/ Pregnancy Avoidance	8. Agrees to use two forms of nonhormonal contraception (dual contraception, as described in Section 4.7) consistently during the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she: …	8. Agrees to use ~~**two forms of nonhormonal**~~ contraception **during the study and for 30 days following the last dose of study drug. Specifically agrees to use** nonhormonal contraception, ~~**(dual contraception**~~ as described in Section 4.7 consistently during the Screening period, and the Randomized Treatment Period **and either nonhormonal or oral contraceptives after return of**	To specify use of contraceptives for 30 days following treatment. Also removed the requirement for dual nonhormonal contraception as spermicide is not available in all countries.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
	c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;	**menses following treatment discontinuation.** However, the patient is not required to use ~~**dual**~~ **specified non-hormonal** contraception if she: … c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of ~~**dual**~~ non-hormonal contraception **as described in Section 4.7**;	
Synopsis: Inclusion Criteria Section 4.3.1 Inclusion Criteria	9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded;	9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: ~~**polyps < 2.0 cm by ultrasound are not excluded;**~~ **Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or <2 cm are eligible;**	To provide clarity.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	4. Has a weight that exceeds the weight limit of the DXA scanner;	4. Has a weight that exceeds the weight limit of the DXA scanner **or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);**	Adds exclusion for any other condition that would interfere with obtaining an interpretable DXA scan.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	6. … A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;	6. … ~~**A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;**~~ **Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;**	To provide clarity.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	13. Has any of the following clinical laboratory abnormalities at any screening visit: … … d. None. e. None.	13. Has any of the following clinical laboratory abnormalities at any screening visit: … d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN); e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN)	Added to exclude patients with conditions that would result in abnormal calcium and phosphorus levels.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	14. Has clinically significant cardiovascular disease including: … e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec; g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;	14. Has clinically significant cardiovascular disease including: … e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec **on the Screening visit or Baseline Day 1 ECG;** g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg ~~**on 2 repeat measures at least 15 minutes apart**~~ or diastolic blood pressure > 100 mmHg **on 2 repeat measures at least 15 minutes apart** at any screening visit or the Baseline Day 1 visit;	To provide clarification on visits for the exclusion criteria. To clarify that both systolic and diastolic blood pressure criteria must be demonstrated on 2 repeat measures.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	16. Has a history of clinically significant condition(s) including, but not limited to the following: … a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded); None.	16. Has a history of clinically significant condition(s) including, but not limited to the following: … a. Untreated thyroid dysfunction ~~**or palpable thyroid abnormality**~~ (patients with adequately treated hypothyroidism who are stable on medication are not excluded); d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;	Deleted as redundant. Untreated palpable abnormality would generally fall under untreated thyroid dysfunction. To add an exclusion criterion for systemic autoimmune disease.
Synopsis:	17. Is currently pregnant or	17. Is currently pregnant or	To clarify the

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Exclusion Criteria Section 4.3.2 Exclusion Criteria	lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;	lactating, or intends to become pregnant **during the study period through 1 month after the last dose of study drug** or **intends** to donate ova during the study period or within 2 months after the last dose of study drug;	pregnancy window.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.	23. Is inappropriate for participation in this study ~~**for other reasons**~~ **because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements,**-as determined by the investigator, sub-investigator, or medical monitor;	To explain circumstances and provide examples when a potential patient would be inappropriate for participation in the study.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	None.	24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.	Added new exclusion criteria to avoid confounding the assessment of hemoglobin.
Synopsis: Secondary Efficacy Endpoints Section 3 Study Objective and Endpoints Section 9.3.2 Statistical Considerations and Data Analyses	The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: … • Proportion of women who achieve amenorrhea over the last 35days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by the alkaline hematin method; None. None.	The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: … • Proportion of women who achieve amenorrhea over the last 35 days of treatment ~~**as measured by the alkaline hematin method;**~~ • None. • Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11;	Time to amenorrhea Endpoint removed due to redundancy. Presenting the amenorrhea rate using a proportion versus a cumulative Kaplan-Meier probability is preferred since it is more consistent with method used for the primary responder endpoint analysis. Added secondary endpoints related to UFS-QOL and PGA for function and symptoms to address the added secondary objectives.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
	None. None. None. None. None. None.	• Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to Week 24;	
Synopsis: Safety Endpoints Section 3 Study Objective and Endpoints	None. • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA;	• Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week~~s~~ **~~12 and~~** 24 in bone mineral density at the **lumbar** spine (~~average of~~ L1-L4), total hip, and femoral neck as assessed by DXA;	Endpoint for assessment of bone mineral density at Week 12 is pre-specified as a separate endpoint with comparison between Group A and Group B. This endpoint will support inclusion of add-back therapy in the treatment regimen.
Synopsis: Exploratory Endpoints Section 3 Study Objective and Endpoints Section 9.6 Exploratory Analyses	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively;	None.	Exploratory endpoints related to UFS-QOL are removed, and secondary endpoints related to assessments of certain components UFS-QOL are added.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 1.1 Schedule of Activities Table 1-1	Visit window timing (days) Week 24 (or Early Termination of Study Drug) ± 10 None. Treatment Compliance Week 4 through Week 24 None. Week 24 (or Early Termination of Study Drug) None. Follow-up None.	Visit window timing (days) Week 24 (or Early Termination of Study Drug): ~~± 10~~ **-10/+20** PGA for function PGA for symptoms Treatment Compliance **and Study Drug Accountability** Week 4 through Week 24 Treatment compliance and drug accountability Week 24 (or Early Termination of Study Drug) Urinalysis Follow-up Temperature collection, pregnancy test, status of menstruation recovery	Visit window expanded to allow transition of eligible patients into open label extension study MVT-601-3003 without interruption. Added new assessments in line with new secondary efficacy endpoints. Updated to clarify the assessment. Added additional assessments for treatment compliance and urinalysis at week 24. Added additional assessments for follow up visit for patients who do not roll-over to the extension study.
Section 1.1 Schedule of Activities Table 1-1 footnotes	d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose pharmacodynamic sample, pregnancy and urinalysis test samples prior to first dose of study drug. The patient must complete MIQ, UFS-QoL, and EQ-5D questionnaires prior other study procedures and prior to first dose of study drug.	d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. **The following procedures must be completed prior to randomization: urine pregnancy, vital signs, waist circumference, weight, temperature, complete physical examination, visual acuity assessment,12-lead ECG, and review of eligibility criteria.** Collect clinical laboratory **sample**, PK sample**,** ~~**pre-dose**~~ pharmacodynamic sample, ~~**pregnancy**~~ and urinalysis prior to first dose of study drug. ~~**The patient must**~~ **Whenever possible,** complete MIQ, UFS-QOL, **PGA for symptoms and PGA for function,** and EQ-5D-	To clarify order of assessments during baseline Day 1 visit.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		5L ~~questionnaires prior other study procedures and~~ prior to the first dose of study drug.	
	e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.	e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit. **The last dose of study drug in the Randomized Treatment Period will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.**	To provide clarity on definition of Week 24 visit and when the last dose is taken.
	h. Visual acuity must be assessed with the study eye chart. The patient should wear any prescription glasses or contacts during the assessment.	h. Presenting visual acuity must be assessed with the supplied study eye chart. **If the** patient **uses corrective lenses, she** should wear **~~any~~her usual** prescription glasses **or contact lenses** during the assessment, **and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions. See Study Reference Manual for additional instructions on visual acuity testing and see Section 6.8.2.8 for overall guidance including follow-up.**	To provide guidance on visual acuity examination and follow-up.
Section 1.1 Schedule of Activities Table 1-1 footnote i Section 6.2.1 Screening 1 Visit Section 6.8.2.3 Physical and Gynecologic Exams	Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit.	Papanicolaou test must be conducted for women without a test result within **~~6 months~~ 2 years** prior to the Screening 1 visit.	Window for Papanicolaou test expanded to approach the guidelines for cervical cancer screening.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 1.1 Schedule of Activities Table 1-1 footnote j	…Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests.	…Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests. **In addition to clinical chemistries and a complete blood count, include thyroid-stimulating hormone at Screening 1. Screening laboratory tests may be repeated during the screening period once, if necessary, at the investigator's discretion. Additional re-testing requires the approval of the medical monitor. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.**	To provide clarification on laboratory tests: to indicate thyroid-stimulating hormone testing at Screening 1, repeats of screening tests, and testing for iron and ferritin in patients with microcytic anemia.
Section 1.1 Schedule of Activities Table 1-1 footnote k	…In addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, Vitamin D, iron, ferritin, and hemoglobin A1c.	…In addition to clinical chemistries and a complete blood count, include a lipid profile, ~~**levels of parathyroid hormone, thyroid-stimulating hormone,**~~ prolactin, Vitamin D, ~~**iron, ferritin,**~~ and hemoglobin A1c.	Parathyroid hormone testing is removed (patients with abnormal calcium and phosphorus will be excluded). Thyroid stimulating hormone level will be obtained at Screening 1.
Section 1.1 Schedule of Activities Table 1-1 footnotes m, n	…Administer study drug after PK and pharmacodynamics sample collections are complete…	…Administer study drug after PK and pharmacodynamics sample collections are complete **(Study drug is not administered at Week 24 Visit; for patients proceeding into the extension study, refer to protocol for study MVT-601-3003).**	Added note at end of footnotes for PK and PK samples clarifying that no study drug is administered at the Week 24 visit
Section 1.1 Schedule of Activities Table 1-1 footnote o Section 6.8.1.11 Pharmacogenomics Sample	Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected.	Pharmacogenomics sample **(unless precluded by local law or regulations)**: a separate pharmacogenomics consent is required before this sample may be collected.	Added note that pharmacogenomics sample will not be obtained if precluded by local laws or regulations

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Collection			
Section 1.1 Schedule of Activities Table 1-1 footnotes	None.	w. Patients not proceeding to the extension study who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will be followed and will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination visit (see Section 6.7). The repeat biopsy will be submitted to the central laboratory.	Added new footnote to provide guidance on scheduling DXA assessments and follow-up for patients not entering the extension study.
	None.	x. Schedule DXA as early as possible within the Week 24/Early Termination visit window. Patients not proceeding to the extension study who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo another DXA scan at 6 (± 1) months after the Week 24/Early Termination visit scan to evaluate recovery and will be contacted about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.	Added new footnote for follow-up procedures for abnormal endometrial biopsy for patients not proceeding into the extension.
	None.	y. Patient will enter responses in a paper questionnaire at the site.	Added new footnote that PGAs for functions and symptoms are completed as a paper questionnaire.
	None.	z. The patient should be asked to bring all study drug to the clinic at each visit. Please refer to section 5.8.	Clarification.
Section 2.2.4.4 Clinical Studies in Women with Uterine Fibroids or	The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to	Adverse drug reactions associated with relugolix in women with uterine fibroids or endometriosis include hot flush, headache, hyperhidrosis and bone	Updated for consistency with the Investigator Brochure.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Endometriosis and Men with Prostate Cancer	relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.	density decreased. Adverse drug reactions associated with relugolix in men with prostate cancer include hot flush, fatigue, arthralgia, nausea, weight increased, gynecomastia and night sweats.	
Section 4.1 Overall Study Design Figure 4-1	Open-Label Extension Study (Eligible Patients) 24 Weeks	Open-Label Extension Study (Eligible Patients) **28** Weeks	Study schematic updated to indicate the open-label extension is 28 weeks instead of 24 weeks
Section 4.1 Overall Study Design Figure 4-2 Figure legend	Bottom scenario: … • Patients whose first screening cycle MBL is < 80 mL and whose second screening cycle menstrual blood loss is > 160 mL will follow the bottom scenario visit schedule Additional Scenarios (not depicted): … • … If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule.	Bottom scenario: … None. Additional Scenarios (not depicted): … • … If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule, **and the patient does not need to collect menstrual blood loss for another cycle.**	Clarification Schematic of Screening Visit Scenarios is updated to indicate that for patient with MBL ≥ 160 mL do not need to collect menstrual blood loss for another cycle.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 4.6 Removal of Patients from Therapy	• Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements.	• Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements. **This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; missing multiple study visits; and persistent (> 2 consecutive months) with < 50% of the required number of days of eDiary completion;** • **Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment;**	To provide definition of gross non-compliance. Add criteria for withdrawal from treatment for patient whose treatment assignment has been unblinded to harmonize with Section 5.7.
Section 4.7 Contraception/ Pregnancy Avoidance	In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply: … The only acceptable methods of dual contraception are: • Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);	In this study, medications and devices containing hormones **for contraception** are excluded, and patients must agree to use ~~**two forms of**~~non-hormonal contraception ~~**(dual contraception)**~~ **throughout the study, including through 30 days following the last dose of study drug**, unless any of the following apply: … The only acceptable methods of ~~**dual**~~ contraception **for those for whom one of the above methods do not apply** are: • Condom **(male or female condom)** with **or without** spermicide (cream, spray, foam, gel, suppository or polymer film);	As the common spermicide, nonoxynol-9 (N-9), is no longer approved in several countries participating in the study and other effective spermicides are not readily available in those countries, the protocol-specified contraceptive methods were reviewed and the use of a condom (male or female) with or without spermicide permitted.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 5.1 Treatments Administered	Each patient will be instructed to take one tablet and one capsule per day.	Each patient will be instructed to take one tablet and one capsule per day. **The last dose of study drug will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.**	Added text to clarify last dose due to transition into extension study (see above).
Section 5.4 Directions for Administration	The study treatment should be taken in the fasted state (other than water) in the morning, at least 1 hour before breakfast. … Patients should take any oral iron supplementation with meals.	The study treatment should be taken in the fasted state (other than water**, tea, or coffee**) in the morning, at least 1 hour before breakfast. … None.	Definition of fasted state for drug administration is clarified to include tea or coffee. Restriction to take iron with meals is removed.
Section 5.5 Dose Reduction/Dose Administration Section 7.1.1 Adverse Event	…Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).	**~~…Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event.~~** Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).	Text removed as it is the investigator's responsibility to determine appropriate management of study drug in a setting of an adverse event
Section 5.6 Storage, Packaging, and Labeling	Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 35°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee).	Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to **~~35°C~~ 25°C** with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). **Study drug should be stored protected from light.**	Modified to be consistent with study drug labeling.
Section 5.7 Blinding	Investigators will have direct access to a given patient's individual study treatment, however, the investigator should make every effort to first contact the medical monitor or appropriate study personnel to discuss options **before** unblinding the patient's treatment assignment.	**~~Investigators will have~~The decision to unblind a patient's treatment assignment in an emergency situation resides with the investigator who has** direct access to **unblind** a patient's individual study treatment; however, the investigator should **~~make every effort~~**attempt to contact the medical monitor or appropriate study personnel to discuss	To provide clarification that the decision to break the treatment code in emergency situation resides with the investigator.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		options before unblinding the patient's treatment assignment **unless the urgency of the medical situation precludes this.**	
Section 5.8 Study Drug Accountability and Treatment Compliance	If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%) it may be appropriate to withdraw the patient from the study.	If a patient is persistently noncompliant with the study treatment **~~(ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%)~~** it may be appropriate to withdraw the patient from the study **(see Section 4.6).**	Revised to align with criteria for removal from therapy.
Section 5.10.1 Prohibited Medications Table 5-3	Anti-convulsant drugs (specified) Examples phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	Anti-convulsant drugs (specified) Examples phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone **Note: All other anticonvulsants are allowed**	Added clarification that other anticonvulsants not listed are allowed.
	Progestins Examples dienogest norethindrone medroxyprogesterone	Progestins **and progestin implants.** Examples dienogest norethindrone medroxyprogesterone **cyproterone** **etonogestrel**	To include additional examples of prohibited medications.
	Estrogen Examples estradiol valerate conjugated estrogens	Estrogen Examples estradiol valerate conjugated estrogens **ethinyl estradiol**	To include additional examples of prohibited medications.
	Oral Contraceptives Examples combined or progestin only	**Hormonal ~~oral~~ contraceptive patches and vaginal rings** Examples combined or progestin only **Nuva Ring**	To include additional examples of prohibited medications.
Section 5.10.1 Prohibited Medications	Bone Agents Window/Comments No prior use if used for reduced	Bone Agents Window/Comments No prior use if used for reduced	Provide a specific clarification that Calcium and vitamin

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Table 5-3	bone mineral density	bone mineral density **Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.**	D are allowed.
Section 5.10.1 Prohibited Medications Table 5-3	P-glycoprotein Inducers Examples carbamazepine rifampin St. John's wort	P-glycoprotein Inducers Examples **avasimibe** carbamazepine **phenytoin** rifampin St. John's wort **tipranavir/ritonavir**	To include additional examples of prohibited medications. Clarify when short term use of these Pgp inducers can be allowed in study.
Section 5.10.1 Prohibited Medications Table 5-3	Moderate and Strong P glycoprotein Inhibitors Examples None. Footnotes None.	Moderate and Strong P glycoprotein Inhibitors Examples amiodarone, atazanavir[f], azithromycin[a], captopril[b], carvedilol[g], clarithromycin[a], cobicistat[f], conivaptan, cyclosporin[c], diltiazem, dronedarone, erythromycin[a], felodipine[d], itraconazole[e], ketoconazole[e], lopinavir/ritonavir[f], quercetin, quinidine,,ranolazine, ticagrelort[g], verapamil Footnotes **a. Roxithromycin is allowed** **b. All other angiotensin converting enzyme inhibitors are allowed** **c. Tacrolimus is allowed** **d. Amlodipine and nifedipine are allowed** **e. Fluconazole is allowed** **f. Integrase inhibitors are allowed** **g. Metoprolol and atenolol are permitted**	To include additional examples of prohibited medications. Clarify when short term use of these Pgp inhibitors can be allowed in study.
Section 6.2.1 Screening Visit 1	The order of procedures should be as follows. …	The order of procedures should be as follows. …	Added new text to provide clarification

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	None. None.	• Complete physical examination and visual acuity assessment • Clinical laboratory tests, including TSH, urinalysis	for the order of procedures.
Section 5.10.2.2 Iron Therapy Section 6.2.1 Screening Visit 1 Section 6.2.2 Screening Visit 2 Section 6.8.2.4 Clinical Laboratory Samples	None. If the hemoglobin is < 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be obtained as an unscheduled test	**If the hemoglobin is < 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.** If the hemoglobin is < 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be **reported through the central lab ~~obtained as an unscheduled test~~.**	Added new text to provide guidance on laboratory diagnosis and management of iron deficiency anemia. For Section 6.2.2 Clarified that iron and ferritin are be reflex labs that will be reported trough central laboratory.
Section 6.2.6 Retesting	None.	Screening laboratory tests may be repeated once during the Screening period, if necessary, at the investigator's discretion. For laboratory-based entry criteria, the most recent value will be used to determine eligibility. Additional laboratory retesting requires the approval of the medical monitor. Retesting of other procedures (except once, as required, due to technical or logistical issues such as an inadequate sample) also require approval of the medical monitor.	New section added to allow single repeat of screening laboratory tests.
Section 6.6 Additional Safety Follow-Up Procedures	None.	For patients not continuing into the extension study (MVT 601-3003), additional safety procedures are required in some circumstances as described below. These procedures will be performed during unscheduled visits. • Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses	New section added to provide guidance for additional safety follow up procedures for patients who do not proceed into extension study.

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		has resumed and questioned about factors that may affect resumption of menses. • Patients with endometrial biopsy findings of endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings during through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory. In addition, patients with endometrial hyperplasia with atypia will be evaluated and managed, as needed, by a gynecologist. • Patients who have had a bone mineral density loss of > 2% at the lumbar spine (average of L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scanning. The follow-up DXA scan will be submitted for central reading.	
Section 6.8.1.2 Transvaginal and Transabdominal Ultrasound	None.	Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone or when endometrium cannot be evaluated or when	Added clarification regarding use of saline or gel contrast for ultrasound.

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		there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.). If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24	
Section 6.8.1.5 Patient Diary	The eDiary data will be reviewed by the investigator to identify any potential adverse events.	The eDiary data will be reviewed by the **study staff.** ~~**investigator to identify any potential adverse events**~~	To ensure consistency with section 7.2 of the protocol stating that eDiary entries will be reviewed by study site personnel.
Section 6.8.1.9 Patient Global Assessment for Symptoms and Patient Global Assessment for Function	None.	These simple questions are used by the patient to qualitatively describe severity of symptoms or effects on function (PGA) (see Appendix 6) on a schedule described in the Schedule of Activities (Section 1.1). With the exception of Baseline Day 1 (see Section 1.1), patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (Section 1.1). With the exception of Baseline Day 1, patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site.	New section added to describe assessments for the newly add PGA secondary objectives.

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Section 6.8.1.10 Status of Menstruation Recovery	After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued.	None.	Menstruation recovery follow up outlined in Section 6.6.
Section 6.8.2.3 Physical and Gynecologic Exams	Visual acuity will be checked at the beginning and end of the study by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment.	None.	Visual acuity assessment instructions moved to a new section.
Section 6.8.2.4 Clinical Laboratory Samples **Table 6-1**	Chemistry Creatinine Kinase Hormones Intact Parathyroid Hormone	Chemistry ~~**Creatinine Kinase**~~ Hormones ~~**Intact Parathyroid Hormone**~~	Parathyroid hormone testing is removed (patients with abnormal calcium and phosphorus will be excluded). "Creatinine kinase" Typographical error removed.
Section 6.8.2.6 Endometrial Biopsy	An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A pipelle should be used to obtain the specimen. A second biopsy is to be performed at the Week 24 visit. The biopsies will be read centrally.	An endometrial biopsy will be obtained using an endometrial suction curette (eg, Pipelle®) and submitted to the central laboratory for reading. If the biopsy is inadequate for diagnosis at either Screening or at Week 24, it should be repeated and sample submitted to the central laboratory. If the second specimen is also inadequate for diagnosis at Screening, the patient is not eligible for the study. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound).	To provide clarification and details for endometrial biopsy.
Section 6.8.2.7 Bone Mineral Density	Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient.	Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient). **The scans will be read by the central radiology laboratory in**	Added clarification of central reading.

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		accordance with the imaging charter.	
Section 6.8.2.7 Bone Mineral Density	The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.	None.	Deleted details on analysis of bone mineral density. This info will be provided in the SAP.
Section 6.8.2.7 Bone Mineral Density	Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the sties assessed during the study. In this case, repeat scan may be required for confirmation of the results, and it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.	Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the **anatomical** sites assessed during the study. In this case, ~~**repeat scan may be required for confirmation of the results, and**~~ **it is at the investigator's discretion to consider the patient's status and determine future management.** Detailed instructions for ~~**bone mineral density monitoring**~~ ~~**DXA scanning**~~ will be provided in the Study Reference Manual. **Please see Section 6.6 for follow-up of patients who are not continuing into the extension study (MVT-601-3003) and whose bone mineral density has decreased by > 2% at the lumbar spine (L1-L4) or total hip at the Week 24/Early Termination visit relative to Baseline.**	Further specified follow-up measures for observed bone mineral density loss.
Section 6.8.2.8 Visual Acuity	None.	Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual	New section created to provide additional details and to align with other studies with relugolix.

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		acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see Study Reference Manual for additional details). Patients whose presenting visual acuity score is 90 or lower at the Baseline visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history. Patients whose presenting visual acuity score at Week 24 /Early termination has decreased by 10 or more points from Baseline should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.	
Section 7.1.1 Adverse Event	Events that do not meet the definition of an adverse event include: … • None.	Events that do not meet the definition of an adverse event include: … • Events of heavy menstrual bleeding, as heavy menstrual bleeding is quantified as an efficacy endpoint, unless the event meets seriousness criteria.	As heavy menstrual bleeding is being assessed as an efficacy endpoint, added it to list of events that do not meet definition of adverse event. Also clarified that would be reportable as an adverse event if met the criteria for seriousness.
Section 7.6 Serious Adverse Event Reporting	Table providing details to send completed Safety Report Forms to PRA Safety & Risk Management	Table updated to send completed Safety Report Forms to **QuintilesIMS**	Updated Contact info for reporting Serious Adverse events. Updates to e-mail and phone number are also included in this section.
Section 7.10 Benefit/Risk Assessment	<u>Impact on Eligibility</u> Exclusion criteria for a history of osteoporosis, osteopenia,	<u>Impact on Eligibility</u> Exclusion criteria for a history of osteoporosis, ~~**osteopenia**~~ ,	Osteopenia is not an exclusion criterion in this study.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Table 7-2	metabolic bone disease, …	metabolic bone disease, …	
Section 7.10 Benefit/Risk Assessment Table 7-2	Hepatic Enzymes	Hepatic Enzyme **Increase**	Updated naming of this potential risk, matching IB nomenclature
Section 9.2 Statistical Considerations and Data Analyses	The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations.	The Per-Protocol Population will consist of those members of the ITT Population who have no **relevant** major protocol violations, **defined as a subset of all major protocol violations (details will be provided in the statistical analysis plan).**	Clarification.
Section 9.3.2 Statistical Considerations and Data Analyses	For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume and time to amenorrhea, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients for whom the first time at which menstrual blood loss of <80 mL AND at least a 50% reduction from baseline is achieved is during a cycle when no feminine products were returned due to amenorrhea absence of a menstrual period, the most recent menstruation stop date will be used. … Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline.	For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume ~~**and time to amenorrhea**~~, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. ~~**Patients for whom the first time at which menstrual blood loss of <80 mL AND at least a 50% reduction from baseline is achieved is during a cycle when no feminine products were returned due to amenorrhea absence of a menstrual period, the most recent menstruation stop date will be used.**~~ … Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, **UFS-QOL score, PGA for function and symptoms, MIQ Score,** Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline.	Changes made to ensure consistency with changes in secondary efficacy endpoints.
Section 9.4 Safety Analyses	None.	To support the inclusion of add-back therapy in the treatment regimen, the safety endpoint of	To provide clarification on analysis plans for

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		mean percent change from Baseline in bone mineral density lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal comparison of Group A versus Group B (see details in the joint statistical analysis plan).	bone mineral density which includes pooling of data across the two replicate studies.
Appendix 6 Patient Global Assessments	None.	Patient Global Assessment (for function) How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? 1. No limitation at all 2. Mild limitation 3. Moderate limitation 4. Quite a bit of limitation 5. Extreme limitation Patient Global Assessment (for symptoms) How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? 1. Not severe 2. Mildly severe 3. Moderately severe 4. Very severe 5. Extremely severe	To support secondary objectives.

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 10-FEB-2017

SPONSOR SIGNATURE PAGE

LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3002

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

13Feb2017
Date

13-Feb-2017
Date

13-Feb-2017
Date

AMENDMENT 1: SUMMARY OF CHANGES

Item; Section(s)	Original	Amendment 1	Rationale
Study Title	An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids	LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids	To add the study moniker
Sponsor Signature Page		Biostatistics and Medical Director signatories added; CEO signatory removed	To update signatories based on personnel additions
Study Schematic 4.1		Updated Figure 4-1	To indicate procedures consistent with the SOA
IC #3; Synopsis, 4.3.1	"Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);"	None	Weight restriction, other than as related to DXA scanner accommodation (covered in EC #4) was not needed.
IC #5 (now IC #4); Synopsis, 4.1, 4.3.1, 6.2, 6.3, SOA footnote q	"Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal ultrasound performed with saline or gel contrast during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria: a. Subserosal, intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter), or b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3"	"Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria: a. Subserosal, intramural, or <50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3; Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size. Note 2: Saline or gel contrast is not	To clarify situations in which a transabdominal ultrasound and saline or gel infusion should be performed

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		required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone."	
EC #5; Synopsis, 4.3.2	Has a baseline bone mineral density z-score < -2.0 at spine or total hip	Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck	To exclude patients with baseline bone mineral density z-score of < -2.0 at femoral neck
Placebo Matching; Synopsis, 5.1	Placebo and active tablets and capsules will matched for size, shape, color, and odor	Placebo and active tablets and capsules will matched for size, shape, and color	Odor is not being specifically tested.
IC #4 (now IC #5); Synopsis, 4.1, 4.2, 4.3, 4.3.1, Figure 4-1, Figure 4-2	"Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period"	"Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL for 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period"	To allow patients who have demonstrated menstrual blood loss that is double or more the screening requirement in a single cycle to enroll based on menstrual blood loss data from only one cycle, rather than two
IC #7 (now IC #6); Synopsis, 4.1, 4.3.1	"…not expected to be a candidate for gynecological surgery or ablation procedures…"	"…not expected to undergo gynecological surgery or ablation procedures for uterine fibroids…"	To clarify the criterion's intent
IC #9 (now IC #8); Synopsis, 4.1, 4.3.1, 4.7	"Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram"	"Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure™ syndrome" in the investigator's opinion)"	To exclude women with the potential confounding factor of post-Essure syndrome

Item; Section(s)	Original	Amendment 1	Rationale
IC #10 (now IC #9); Synopsis, 4.1, 4.3.1	"Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer)"	"Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded."	To remove endometritis as an exclusion and to make polyp exclusion consistent with other entry criteria
IC #11 (now IC #10); Synopsis, SOA footnote p, 4.1, 4.3.1, 6.2.1, 6.2.2	"If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period."	"If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period."	To align with recommended mammography screening intervals, accounting for an ~6-month Treatment Period; Disallow patients with BI-RADS 3 readings due to their higher risk
IC #12; Synopsis, 4.3.1	A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.	None	To define the use of randomization authorization in the study procedural documents rather than in the protocol

Item; Section(s)	Original	Amendment 1	Rationale
EC #1; Synopsis, 4.1, 4.3.2, 6.2, SOA footnote q	"Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment."	"Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥2.0 cm, large simple ovarian cyst >4.0 cm, endometrioma(s) >4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study. Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (e.g., suspected intrauterine masses, equivocal endometrial findings, etc.)."	To add examples of common findings that would be considered exclusionary; To clarify situations in which saline or gel infusion should be performed; To allow patients with finding not requiring immediate evaluation or treatment to enroll
EC #2; Synopsis, 4.3.2	"Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle"	"Has known rapidly enlarging uterine fibroids in the opinion of the investigator"	To remove an exclusion that may be a disease-state manifestation and to add an exclusion for uterine fibroids at higher risk to be malignant
EC #10g, h; Synopsis, 4.3.2	none	"Migraine with aura" "History of porphyria"	To add migraine with aura as an example of a contraindication to treatment with low-dose estradiol and norethindrone acetate and to add an exclusion for porphyria, which is listed in the prescribing information in some countries

Item; Section(s)	Original	Amendment 1	Rationale
EC #12; Synopsis, 4.3.2	"Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study."	"Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative."	To incorporate high-risk human papilloma virus reflexive testing that will be performed by the central laboratory into the criterion
EC #14b, d, h; Synopsis, 4.3.2	"History of angina" "History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute)" "Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram"	"History of angina or significant coronary artery disease (i.e. ≥50% stenosis)" "History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute)" Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness"	To add an exclusion for significant coronary artery disease (#14b), to remove the exclusion for pacemaker (criterion was internally inconsistent) (#14d), and to allow for physiologically appropriate bradycardia in physically-fit patients (#14h)

Item; Section(s)	Original	Amendment 1	Rationale
EC #16c; Synopsis, 4.3.2	"History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year)"	"Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled."	To broaden the ability for patients with remote psychiatric disorders and current psychiatric disorders who are able to participate in the trial to be enrolled
EC #17; Synopsis, 4.3.2	"Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study"	"Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug"	To clarify timing relative to last dose of study drug
Study Completion; 4.6	None	Added definition of study completion (completion of Week 24 visit)	To include a definition

Item; Section(s)	Original	Amendment 1	Rationale
Removal of Patients from Therapy; 4.6, 6.7.2.6	Patients who have percent change from Baseline in bone mineral density at either the Week 12 or Week 24 visit (or any unscheduled visit) at the lumbar spine (average L1-L4), total hip, or femoral neck of < -4.0 that is repeated and confirmed (ie, both values are < -4.0)	Replaced with alert notifications from the central radiology readers to the investigator for a 7% or greater decline in bone mineral density at any time point (added to section 6.7.2.6)	To allow for use of clinical risk assessment by the investigator in determining whether withdrawal is warranted and determination of future management. The study is conducted in patients generally considered at low risk for fracture; Patients with history of osteoporosis, or baseline bone mineral density Z-scores < -2.0 are excluded.
Identification of Investigational Product; 5.0. Table 5-1	No color listed Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™ or Activelle™).	"Swedish orange" added in the description for the placebo and active low-dose add back capsule Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™ or Activelle™).	To add product details
Product Characteristics; Section 5.2.1	Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the United States Pharmacopeia and the National Formulary (USP/NF) excipients.	"Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients. Placebo to match relugolix is a pink tablet using common excipients."	To facilitate review of the protocol in European countries, USP language was made more general

Item; Section(s)	Original	Amendment 1	Rationale
Study Drug Storage; 5.6	"Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 1°C to 30°C until it is used or returned to the sponsor (or designee)."	"Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 25°C with excursion to 15°C to 30°C permitted, until it is used or returned to the sponsor (or designee)."	To narrow the storage temperatures for both relugolix/placebo and estradiol/ norethindrone to match the temperature requirements for Activella
Study Drug Administration; 5.4, 6.3	None	Fasting does not require withholding of water. On clinic visit days that are not in the morning, patients should fast for at least 2 hours prior to the visit and for 1 hour taking the study drug.	To provide clarifications on study procedures
Blinding; 5.7	Investigator to determine if treatment assignment of a site-unblinded patient should be revealed to the sponsor. Sponsor may unblind for a serious adverse event.	Investigator not to reveal treatment assignment of a site-unblinded patient to the sponsor. Sponsor unblinding for serious adverse events described in the Safety Management Plan.	To make this decision a sponsor responsibility; To provide details and context for unblinding of serious adverse events by the Sponsor in the Safety Management Plan, rather than in the protocol
Prohibited Medications; 5.10.1	None	Contact the medical monitor for approval and guidance on study drug administration if a short course of a prohibited P-glycoprotein inhibitor or inducer is required during the study	To provide additional guidance for such situations
Prohibited Medications; 5.10.1	None	Addition of bazedoxifene, zoledronic acid, and factor Xa inhibitors to Table 5-3	To include additional examples of prohibited medications
Prohibited Medications; 5.10.1	Oral contraceptive exclusion period 2 months	Oral contraceptive exclusion period typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months	To shorten exclusionary period for patients following resumption of menses

Item; Section(s)	Original	Amendment 1	Rationale
Prohibited Medications; 5.10.1	Selective progesterone receptor modulator exclusion period 2 months	Selective progesterone receptor modulator exclusion period 6 months	To avoid possible confounding related to the endometrial effects of these drugs
Prohibited Medications; 5.10.1	Bone agent exclusion period 2 months prior to Screening	Bone agent exclusion period indefinite if used for low bone mineral density	To make consistent with eligibility criteria
Prohibited Medications; 5.10.1	None	Addition of 1-week exclusionary window for over the counter and herbal products with known hormonal activity	To reduce possible confounding of efficacy and safety due to these products
Analgesic Medications; 5.10.2.1	Specific required medications for uterine fibroid pain and other pain	Requirements changed to recommendations for allowed medications for uterine fibroid pain. Restriction on analgesics for other pain conditions removed.	To liberalize restrictions based on site feedback while encouraging consistency in analgesic use
Adverse Event Reporting Period; 6.2, 7.2.1, SOA footnote f	Non-serious adverse events occurring after signing of the informed consent form and prior to start of study drug should be recorded as medical history	Non-serious adverse events occurring after signing of the informed consent form and prior to start of study drug should be recorded as adverse events rather than medical history if they are considered related to study procedures; otherwise, they should be recorded as medical history.	To capture study procedure-related adverse events as adverse events
Waist Circumference; SOA, 6.3. 6.7.2.1	None	Waist circumference measured at Baseline Day 1	To obtain data to characterize patients with metabolic syndrome
Ultrasound Procedures; 6.2	None	Addition of clarification that the investigator, rather than the central reader, will determine if any exclusionary pathology is present.	Clarification
Pathology Specimens; SOA footnotes i and r, 6.2, 6.3, 6.7.1.3	Whether the Papanicolaou test and would be locally or centrally read was not specified Endometrial biopsy to be read locally (or centrally read if requested)	Papanicolaou test and endometrial biopsy will be centrally read	To improve consistency of readings and to facilitate site logistics
Unscheduled	None	Reminder add to obtain unscheduled iron studies at Visit 2 if hemoglobin	To improve adherence to the

Item; Section(s)	Original	Amendment 1	Rationale
Iron Studies; 6.2		is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal.	protocol requirements
Pre-Screening Procedures; 6.2	Pre-screening procedures	None	To allow sites to utilize site-specific practices for pre-screening
Re-Screening Procedures; 6.2, SOA	None	Certain screening procedures do not need to be repeated for patients who re-screen within 10 weeks of the signing the original informed consent form: transvaginal ultrasound, endometrial biopsy, and bone densitometry.	To reduce patient procedural burden
Early Termination Procedures; 6.5, SOA footnote s	None	Certain early termination visit procedures are not required for patients whose last dose of study drug is during Week 6 or earlier (transvaginal ultrasound, endometrial biopsy, and bone densitometry). These procedures may be done if they will aid in the evaluation of an ongoing adverse event	To reduce patient procedural burden
Unscheduled Visit Procedures; 6.6, SOA	List of procedures to be done to further evaluate adverse events	Adverse events are to be evaluated and concomitant medications, and reason for visit are to be recorded. Other procedures may be done as needed.	Clarification of required and optional procedures at Unscheduled Visits
Clinical Laboratory Tests; 6.7.2.4, Table 6-1, SOA footnote j	Subset of central laboratory tests	All central laboratory tests	To include full list of clinical laboratory tests and to add Vitamin D at Baseline Day 1
Bone Mineral Density; 6.7.2.6	Incomplete details of bone mineral density acquisition and reporting included in this section.	Details of bone mineral density acquisition and reporting moved to the imaging charter.	To have a single document with the full details of this procedure
Endometrial Biopsy 6.7.1.3	None	Specification that a pipelle should be used for the endometrial biopsy	To have greater uniformity in the specimen acquisition
Pregnancy; 7.2		Requirement for reporting partner pregnancies removed	All study patients will be women

Item; Section(s)	Original	Amendment 1	Rationale
Serious Adverse Event Logistics; 7.6	None	Contact information for serious adverse event reporting added	To update with the serious adverse event vendor's logistical details
Safety Analyses; 9.4	The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5% or 6% by body area (lumbar, total hip, and femoral neck) will be estimated with 95% confidence intervals by treatment group. The number and percentage of patients meeting a T-score of < -2.5 by body area will also be estimated with 95% confidence interval by treatment group.	The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar, total hip, or femoral neck) will be estimated with 95% confidence intervals by treatment group.	To align with the statistical analysis plan and remove references to analyses based on cut-offs for T-scores; analyses based on Z-scores will be detailed in the SAP
Schedule of Papanicolaou Testing; SOA	Screening and Week 24/Early Termination	Screening	Procedure not needed because cervical dysplasia not a safety risk in this trial
Schedule of PD Measurements; SOA	Screening 1 visit, Day 1, Weeks 4, 8, 12, 16, 20, 24, and Follow-up	Day 1, Weeks 4, 12, 24, and Follow-up	To remove unneeded sampling time points
Visit Windows; SOA, Figure 4-2, 6.2	Screening 3 visit: Window $\leq$ 10 days after Screening 2 visit Transvaginal ultrasound, gynecology examination, papanicolaou test, endometrial biopsy, mammogram, bone densitometry: Visit 3 Screening 1, 2, and 4 visits to occur within 4 days of end of menses and Baseline Day 1 visit to occur within 4 days of end of menses	Screening 3 visit: Window $\leq$ 15 days after Screening 2 visit. Transvaginal ultrasound, gynecology examination, papanicolaou test, endometrial biopsy, mammogram (schedule appointment), bone densitometry (schedule appointment): Visit 1 Screening 2 and 4 visits to occur within 5(+2) days of end of menses. Screening visit 1 not timed with menses. Screening 4 visit may be skipped if menstrual blood loss with the first cycle collection is $\geq$160 mL.	To improve site logistics and to accommodate turnaround time for patients collecting 1 cycle of menstrual blood loss

Item; Section(s)	Original	Amendment 1	Rationale
Schedule of Visual Acuity Testing and eDiary; SOA footnote u and v, 6.2	Visual acuity at Screening and on Day 1 eDiary: dispense at Screening 3 visit	Visual acuity on Day 1 Paper diary: dispense at Screening 1 visit eDiary: dispense at Screening 1 visit	To remove an unneeded procedure; visual acuity is not an eligibility criterion; therefore, not needed at Screening To allow fuller data capture of menses dates and daily feminine product use
eDiary; Appendix 2	eDiary question text	eDiary screenshots, which also include analgesic medication dose, route, and frequency questions	To update with final e-diary content
UFS-QoL; Appendix 4			To update with correct version of the instrument
CTCAE and IB version; 2.4.2.2 and various	CTCAE, Version 5.0 IB Version 9.0, dated 09 November 2016	CTCAE version not specified in protocol, but the version to be used will be in the study reference manual and noted in the statistical analysis plan.	CTCAE version 5.0 not yet published at the time of study start; IB version removed to avoid discrepancies that may occur when IB is updated during the study
Minor Edits; Various		Corrections of typos, minor clarifications, minor inconsistencies, and minor wording changes	To improve readability and understandability.

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CEO, Chief Executive Officer; CTCAE, Common Terminology Criteria for Adverse Events, DXA, dual x-ray absorptiometry; EC, exclusion criterion; IB, investigator brochure; IC, inclusion criterion; PD, pharmacodynamic; SOA, schedule of activities; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 10-FEB-2017

SPONSOR SIGNATURE PAGE

LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3002

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

13Feb2017
Date

13-Feb-2017
Date

13-Feb-2017
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
EQ-5D	European Quality of Life Five-Dimension Five-Level
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menstrual Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart

Term	Explanation
PD	pharmacodynamics
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3002
Location	Multinational, including North and South America, Europe, and Australia
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	<u>Primary Efficacy Objective</u> • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. <u>Secondary Efficacy Objectives</u> • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.
	Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.

Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during 1 cycle during the screening period. During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). Feminine products will

be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
   a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
   b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

      Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

      Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone;
5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;

7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently during the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study.

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;

9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, $\geq$ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate $\geq$ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;

g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;

h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;

15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary window periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color.
Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. Primary Efficacy Endpoint • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume. Safety Endpoints • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations (Cτ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.

	Exploratory Endpoints • Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of 260 (130 patients in each of the relugolix and placebo arms) will provide > 99% power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients

with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3002

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)		Within 5 (+2) days after completion of Screening 1 menses	Within ≤ 15 days after Screening 2 visit	Within 5 (+2) days after completion of 2nd Screening menses	Within 7 days of the start of menses	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X[e]	X
Waist circumference					X								
Height	X												
Weight	X				X						X	X[e]	X
Temperature	X				X						X	X[e]	
Adverse Event Collection[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity[h]					X						X	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Complete Physical excluding GYN Examination	X				X						X		
GYN Examination with Pap Test, if applicable	X[i]												
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X[e]	X
12-Lead Electrocardiogram			X		X			X			X	X[e]	X
Clinical Laboratory Tests[j]	X	X			X[k]	X	X	X	X	X	X[l]	X[e]	X
PK Sample[m]					X	X		X			X	X[e]	
PD Sample[n]					X	X		X			X	X[e]	X
Daily Study Drug Administration					X							X[e]	
Administer Dose of Study Drug in Clinic					X	X	X	X	X	X	X	X[e]	
PGx Sample[o]					X							X[e]	
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X	X[e]	
Urinalysis	X				X							X[e]	
Mammogram[p]	schedule	X											
Transvaginal Ultrasound (with or without Transabdominal Ultrasound)[q]	X										X[s]	X[e]	
Endometrial Biopsy	X[r]										X[r,s]	X[e]	
Bone Densitometry[t]	schedule	X						X			X[s]	X[e]	
Randomization					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X		X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Dispense Study Treatment					X	X	X	X	X	X		X[e]	
Patient paper diary/ eDiary[u]	X	X	X	X	X	X	X	X	X	X	X	X[e]	
Feminine Product Collection and Venous Blood Sample[v]		X		X		X	X	X	X	X	X	X[e]	
MIQ					X	X	X	X	X	X	X	X[e]	
UFS-QoL					X			X			X	X[e]	
EQ-5D					X						X	X[e]	
Treatment Compliance						X	X	X	X	X	X	X[e]	
Status of Menstruation Recovery													X

Notes:
Abbreviations: EQ-5D, European Quality of Life Five-Dimension Five-Level Scale; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; GYN, gynecology; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life
For patients who are re-screening, please see Section 6.2.6 for abbreviated screening procedures.

a. The screening period should be initiated after the informed consent form is signed and any exclusionary windows for prohibited medications has been confirmed.
b. Visit to occur within 5 (+2) days of the completion of menses. Visit 4 should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.
c. Visit to occur within ≤ 15 days after Screening 2 visit; eDiary dispensation must occur at least 7 days prior to Baseline Day 1. The alkaline hematin menstrual blood loss collection may be repeated once at the discretion of the investigator if one menstrual cycle does not meet menstrual blood loss criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose pharmacodynamic sample, pregnancy and urinalysis test samples prior to first dose of study drug. The patient must complete MIQ, UFS-QoL, and EQ-5D questionnaires prior other study procedures and prior to first dose of study drug.
e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
f. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003) and/or terminate early from the study, a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational

agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~4 weeks after an Early Termination visit).

g. Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure) through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first.
h. Visual acuity must be assessed with the study eye chart. The patient should wear any prescription glasses or contacts during the assessment.
i. Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit. The specimen should be submitted to the central laboratory during screening. Another test should be performed for inadequate or false-positive results and be submitted to the central laboratory.
j. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests.
k. At the Baseline Day 1 visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, Vitamin D, iron, ferritin, and hemoglobin A1c. An additional sample will be collected at this visit in all patients and stored for possible future testing for presence of hepatitis A, B, and C if required per request from medical monitor to assess etiology of liver test abnormalities.
l. At the Week 24 visit or Early Termination visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.
m. Pharmacokinetics samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics sample collections are complete.
n. Pharmacodynamic samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Early Termination and Follow Up visits when no dose is administered).
o. Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive).
p. Patients ≥ 39 years of age at the time of the anticipated Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period; if not, schedule at the Screening 1 visit.
q. Transvaginal ultrasound with or without transabdominal ultrasound must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm. Results must be submitted to and uterine fibroid criteria confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is required. See inclusion criterion #5 and exclusion criterion #1 for guidance as to when to perform a transabdominal ultrasound and saline or gel contrast. If saline or gel contrast is performed at Screening, it should also be performed at Week 24.
r. Obtain sample with a pipelle. Endometrial biopsy is performed at Screening 1 visit in all patients (and at Week 24 visit only if indicated [endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound]) and submitted to the central laboratory.

s. Procedure not required at the Early Termination Visit in patients whose last dose of study drug was during Week 6 or earlier. The procedure may be done if it will aid in the evaluation of an ongoing adverse event.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results will be available prior to randomization. Schedule the test at or shortly after the Screening 1 visit. Bone densitometry should be completed prior to the Screening 3 visit and as early as possible to ensure results are available prior to randomization.
u. Patient paper diary: Patients enter diary information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit. Patient eDiary: Ensure that eDiary data collection begins at least 7 days prior to Day 1. Patients enter eDiary information on a daily basis for their compliance with (study treatment starting at Baseline/Day 1), menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening 3 visit and compliance with study treatment starting at Baseline/Day 1 through Week 24 or Early Termination.
v. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which

are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotropin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies (including 1 in women with uterine fibroids and 1 in women with endometriosis) have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least 1 dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations of estradiol in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

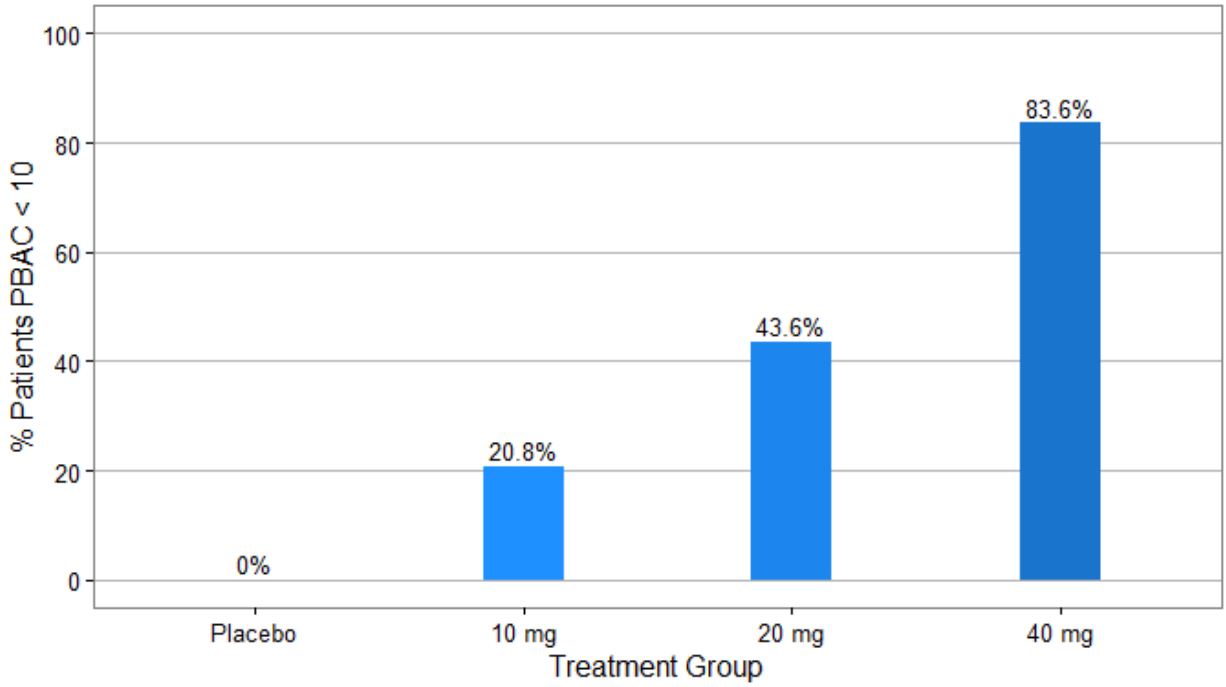
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 19%. The exposure of relugolix is increased by inhibitors

of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 final analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤ 50 ng/dL) and maintained these levels through at least 24 weeks. These 24-week data were comparable to testosterone levels achieved by leuprolide 22.5 mg administered by injection every 3 months. Study C27003 also demonstrated rapid and sustained suppression of testosterone levels by relugolix for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
Primary Efficacy	
• To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by

Objective(s)	Endpoint(s)
	the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks.	• Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.

Objective(s)	Endpoint(s)
Pharmacokinetic and Pharmacodynamic	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.
Exploratory	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or the placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by a centrally-reviewed transvaginal ultrasound (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or

≥ 160 mL for 1 cycle collected during the screening period. During the randomized treatment period, study participants will take blinded study drug orally once daily for 24 weeks. Women with iron-deficient microcytic anemia with a hemoglobin ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at the Screening visit.

A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. A repeat endometrial biopsy will be performed at Week 24 only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Samples will also be collected for PK assessment of relugolix, estradiol, and norethindrone, and for the pharmacodynamic assessment of LH, FSH, estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit to assess safety approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits are provided in Figure 4-2.

Figure 4-1 MVT-601-3002 Study Schematic

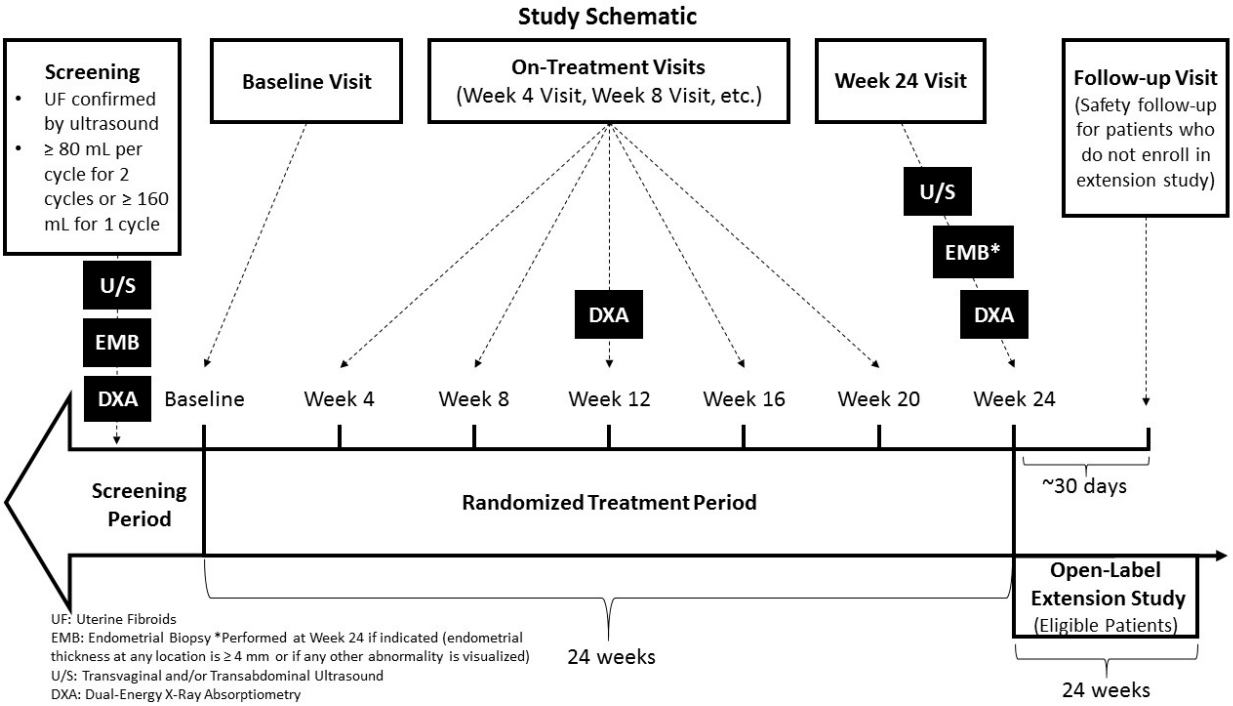


Figure 4-2 Schematic of MVT-601-3002 Screening Visit Scenarios

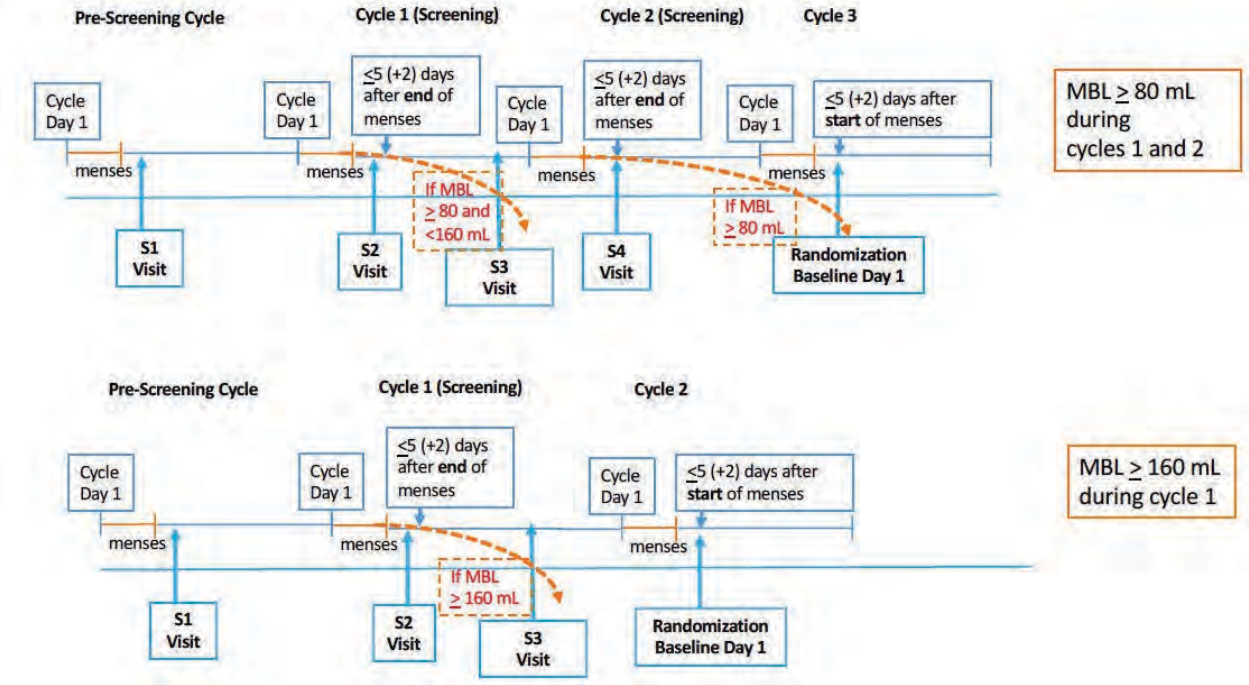


Figure 4-2

Screening visit 1 may be conducted at any time during the pre-screening cycle.

Top scenario:

- Eligibility is based on 2 consecutive screening cycles, each with ≥ 80 mL of menstrual blood loss assessed by the alkaline hematin method where the first screening cycle menstrual blood loss is also < 160 mL.

Bottom scenario:

- Eligibility is based on first screening cycle with ≥ 160 mL menstrual blood loss assessed by the alkaline hematin method.
- Patients whose first screening cycle MBL is < 80 mL and whose second screening cycle menstrual blood loss is ≥ 160 mL will follow the bottom scenario visit schedule.

Additional Scenarios (not depicted):

- Patients whose first screening cycle menstrual blood loss is < 80 mL and whose second screening menstrual blood loss is ≥ 80 mL but < 160 mL may collect menstrual blood loss during a third screening cycle if the first collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is ≥ 80 mL but < 160 mL and whose second screening menstrual blood loss is < 80 mL may collect menstrual blood loss during a third screening cycle if the second collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is < 80 mL may collect menstrual blood loss during a second cycle if the first collection was believed to be inadequate in a highly motivated patient. If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule.

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This study will focus on the primary objective of demonstrating a reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study is designed to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An extension study is planned to provide additional safety and efficacy data through 48 weeks.

Women with uterine fibroids and heavy menstrual blood loss by the alkaline hematin method of ≥ 80 mL/cycle for two cycles or ≥ 160 mL in one cycle during screening will be enrolled in this study. Randomization will be 1:1:1. Placebo was selected as the appropriate control for the study because there is no standard of care medical therapy for the long-term treatment of women with uterine fibroids and heavy menstrual bleeding. Commonly-used treatment options range from combined oral contraceptive pills, which are not effective in many cases, levonorgestrel-containing intrauterine devices, and leuprolide therapy indicated for 3 months in the preoperative setting.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. This dose was selected for evaluation in phase 2 clinical studies based upon phase 1 data demonstrating similar estradiol and progesterone suppression in women treated with single doses of relugolix 40 mg or 80 mg, and data demonstrating that premenopausal women treated with multiple doses of 40 mg once daily relugolix over 14 days had estradiol levels suppressed to a median value of 3.68 pg/mL.

Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, as described above, a phase 2 study of doses of relugolix 10, 20 and 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not

provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 48 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 48 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 1992; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the US as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate has demonstrated that this dose of add-back therapy maintains serum estradiol in the 25-50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy and is not included as a control arm as it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in a well-designed

large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study will primarily assess the efficacy and safety of relugolix 40 mg co-administered with a low-dose of estradiol and norethindrone acetate compared with placebo at 24 weeks to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes. An additional arm with monotherapy relugolix administered for 12 weeks followed by 12 weeks of relugolix co-administered with low-dose hormonal add-back therapy is included to provide data on the requirement for hormonal therapy to mitigate the adverse relugolix side effects of bone mineral density loss and hot flushes.

All eligible women who complete the 24-week study will be offered the opportunity to enroll in an open-label extension study to obtain long-term safety and efficacy data over an additional 28 weeks of treatment, providing approximately 1 year of safety data on the women originally randomized to relugolix.

4.3. Selection of Study Population

The study population will include approximately 390 premenopausal women aged 18 to 50 years with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for randomization and enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Baseline Day 1 visit, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;

4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

    Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

    Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone.
5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently, the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion;
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps ≤ 2.0 cm by ultrasound are not excluded;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;

10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;

18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

4.5. Method of Assigning Patients to Treatment Group and Patient ID Number

After a patient is screened, the investigator determines that the patient is eligible for enrollment, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient's Baseline Day 1 visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient Identification Number.

4.6. Removal of Patients from Therapy

Completion of the Week 24 defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;

- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of dual contraception are:

- Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 2 months following the last dose of study drug.

A patient may start hormonal contraception 4 weeks after her last study dose of study drug provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including just prior to receiving first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

Each patient will be instructed to take one tablet and one capsule per day.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, and color. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

Table 5-1 Description of MVT-601-3002 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An Swedish orange, over-encapsulated round film-coated white tablet with placebo back-fill material	A Swedish orange capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients.

Placebo to match relugolix is a pink tablet using common excipients.

The fixed-dose combination tablet of estradiol 1.0 mg and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3002 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with relugolix placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule for 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state (other than water) in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

On clinic days, patients should be instructed not to eat or drink (other than water) prior to their clinic visit if the appointment is in the morning. If the appointment is later in the day, patients should not eat for at least 2 hours before the appointment and should also not to eat or drink (other than water) for at least 1 hour after administration of the study drug.

Patients should take any oral iron supplementation with meals.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 35°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix, the estradiol/norethindrone acetate combination, relugolix placebo, and the estradiol/norethindrone acetate placebo to be distributed will meet all applicable requirements of the US FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Relugolix 40 mg and relugolix placebo will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate or estradiol/norethindrone acetate placebo.

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding by the investigator for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient's individual study treatment, however, the investigator should make every effort to first contact the medical monitor or appropriate study

personnel to discuss options **before** unblinding the patient's treatment assignment. If unblinding by the investigator occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient. Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment.

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and prior to each visit, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused and used study drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zolendronic acid	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	1 month

Drug Class	Examples	Window/Comments
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone	2 months (6 months for depot subcutaneous or intramusclar injections)
Estrogens	estradiol valerate conjugated estrogens	2 months (6 months for depot subcutaneous or intramusclar injections)
Oral Contraceptives	combined or progestin only	1 month for patients reporting a typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	1 week
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	No prior use if used for reduced bone mineral density
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin tranexamic acid vitamin k preparations factor Xa inhibitors	1 month

Drug Class	Examples	Window/Comments
Glucocorticoids	prednisolone or prednisone dexamethasone	No window Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (≤ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	carbamazepine rifampin St John's wort	2 weeks Patients requiring a short course of these drugs during the study must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporin diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole lopinavir/ritonavir quercetin quinidine ranolazine ticagrelort verapamil	2 weeks (6 months for amiodarone) Patients requiring a short course of these drugs during the study must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

From the Screening 1 visit to the Week 24 (or Early Termination) visit, the recommended analgesics for uterine-fibroid associated pain are as follows:

- First-line: ibuprofen
- Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
- Third-line: opioid or opioid-acetaminophen combination
- Fourth-line: investigator discretion

The purpose of these recommendations is to standardize, to the extent possible, analgesic medication use to facilitate the effects on the secondary endpoint regarding of uterine-fibroid-related pain.

Patients should be instructed not to use analgesics for prophylactic purposes.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL but ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.7. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities in the study synopsis (see Section 1.1). The study is divided into three periods: screening period, randomized treatment period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study; unscheduled visits may also occur as needed to evaluate patients).

6.2. Screening Period

Patients should have a diagnosis of uterine fibroids and a history of heavy menstrual bleeding with or without associated pain on a background of generally regular menses (ie, regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next menstrual period) as reported by the patient for at least 3 months prior to the Screening 1 visit.

The screening period consists of the Screening 1, 2, 3, and 4 visits.

See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening. The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.

6.2.1. Screening 1 Visit

The Screening 1 visit will be conducted following the signing of the informed consent form and may occur at any time during the menstrual cycle. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications, study procedure-related adverse events and any serious adverse events. In addition, vital signs, height, weight, temperature, a complete physical examination, gynecology examination, ultrasound, endometrial biopsy, Papanicolaou test (if needed), clinical laboratory tests, urinalysis, and a urine pregnancy test will be done. Feminine products will be dispensed with instructions to collect and return all products used during the next menses. The paper diary will also be dispensed at this visit and should be completed daily starting with this visit. The bone mineral density scan and mammogram should be scheduled at this time (or within a few days of this visit). Bone densitometry should be scheduled to be prior to the Screening 3 visit and as early as feasible to ensure results are available prior to randomization.

The order of procedures should be as follows. Patients not meeting eligibility criteria after any procedure should not undergo subsequent procedures.

- Medical history and review of prior uterine imaging studies
- Review of concomitant medications (including supplements and over the counter medications)
- Review of inclusion and exclusion criteria
- Urine pregnancy test
- Vital signs, weight, and height

- Ultrasound – do not proceed with additional procedures if no uterine fibroids are identified with the local/initial reading
- Gynecology examination, Papanicolaou test (if need), endometrial biopsy
- Clinical laboratory tests, urinalysis
- Dispense feminine products and paper diary with instructions to begin recording starting information daily, starting on the Screening 1 visit day
- Schedule mammogram (if needed)
- Schedule bone densitometry

The ultrasound will be a transvaginal ultrasound (with or without a transabdominal ultrasound (see Section 4.3 ultrasound entry criteria), performed to assess for uterine fibroids. Saline or gel contrast may be used but is not required (see Section 4.3 ultrasound entry criteria). The anatomic location and size of the fibroid disease will be estimated by the local reader. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to randomization). The investigator, rather than the central reader, will determine if any exclusionary pathology is present. If ultrasound fails to demonstrate fibroids on the local reading, do not proceed with additional Screening visit 1 procedures.

The Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit and the specimen is to be submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

The endometrial biopsy will be obtained using a pipelle and submitted to the Central Laboratory.

The mammogram must be done in patients ≥ 39 years of age by the time of the (anticipated) Baseline Day 1 visit if there is no record (and reading) from within 6 months prior to the screening period.

6.2.2. Screening 2 Visit

Screening 2 visit is scheduled to occur within 5 (+2) days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine products. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine products will be dispensed for collection of menstrual blood loss during the next menses. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be obtained as an unscheduled test. Women whose laboratory testing reveals iron-deficiency anemia as defined in the study must be started on iron therapy.

Confirm the scheduling of the bone densitometry and mammogram (if needed) and review mammogram results, if available. The mammogram must be normal (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) in order for the patient to be eligible.

Once the menstrual blood loss results from the first cycle are available, schedule Screening 3 visit as soon as feasible and within 5 (+2) days of receiving results showing that the menstrual blood loss is ≥ 80 mL.

Patients will be dispensed feminine products to be gathered for the second cycle.

6.2.3. Screening 3 Visit

The patient will return for the Screening 3 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL and within ≤ 15 days after the Screening 2 visit. At the Screening 3 visit, review of inclusion and exclusion criteria will be conducted confirmation of continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. At this visit, review the endometrial biopsy results and review mammogram results, if available. Confirm that the bone densitometry scans have been submitted for central reading. The mammogram and central bone densitometry results must be available prior to randomization.

6.2.4. Screening 4 Visit

The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle. If not skipped, then the Screening 4 visit is scheduled to occur within 5 (+2) days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn for hemoglobin assessment. The patient's eDiary data collection will be reviewed. Laboratory and imaging evaluations will be reviewed to ensure eligibility for randomization.

6.2.5. Menstrual Blood Loss Repeat Collection

At the discretion of the investigator, the collection of menstrual blood loss can be repeated once during the screening period (either after the first or second screening cycle) if one menstrual cycle does not meet the heavy menstrual bleeding alkaline hematin criteria and it is thought to be due to an inadequate collection by a highly motivated patient.

6.2.6. Re-Screening

Patients who fail screening may be re-screened with approval of the medical monitor. Patients undergoing re-screening will sign a new informed consent form and issued a new screening number. For patients who begin re-screening within 10 weeks of signing the original informed consent form, transvaginal ultrasound, endometrial biopsy, and bone densitometry do not need to be repeated, if performed previously.

6.3. Randomized Treatment Period (Baseline to Week 24)

At the Baseline Day 1 visit, patients will be randomized to one of the three study treatment arms (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the Week 24 visit. Patients will continue recording daily in their eDiary. On-treatment study visits will occur every 4 weeks through the end of Week 24. At each post-baseline visit, patients will return their feminine products for alkaline hematin testing. Safety monitoring including signs and symptoms directed physical examination, waist circumference, ECGs, clinical laboratory tests, pregnancy tests, and

adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12 and Week 24 visits. A repeat transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. An endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). The endometrial biopsy will be read centrally. Study drug and eDiary compliance will be reviewed at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the randomized treatment period.

Sites should try to schedule patient visits during the morning, instructing patients to arrive before taking their study drug to allow for pre-dose PK/pharmacodynamic sampling. Patients must come to the clinic in the fasted state (eg, nothing to eat or drink other than water after midnight the day before the clinic visit) for the Baseline Day 1 and Week 24/Early Termination visits.

For visits other than Baseline Day 1 and Week 24/Early Termination, if the clinic visit cannot be scheduled for the morning, patients may eat in the morning but should not have eaten or had anything to drink other than water for at least 2 hours prior to the clinic visit and must not eat or drink (other than water) for at least 1 hour after the clinic visit. In these situations, the laboratory requisitions must indicate that the patient was not fasted for their chemistry and lipid testing.

6.4. Continuation into Extension Study

It is expected that most patients will enter the 28-week extension study (MVT-601-3003), which will be conducted under a separate protocol. Patients will provide separate informed consent to participate in the extension study during which all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate.

6.5. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 24 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 24; however, for patients whose last dose of study drug is during Week 6 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound), endometrial biopsy, and bone densitometry. These procedures may be performed, however, at the investigator's discretion, if they aid in follow-up of ongoing adverse events.

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3003), will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation. Patients who withdraw early from this study will also undergo the Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Refer to the Schedule of Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, PK and pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.7. Study Procedures

6.7.1. Efficacy-Related Procedures

6.7.1.1. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.7.1.2. Transvaginal and Transabdominal Ultrasound

Transvaginal with or without transabdominal ultrasound with or without saline or gel contrast is performed for the diagnosis of uterine fibroids, to determine uterine and myoma volumes, and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Transvaginal ultrasound will be performed. Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = D1 x D2 x D3 x π / 6
Where:
D1 = the longest diameter of the myoma or uterus (unit of length: cm)
D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

6.7.1.3. Endometrial Biopsy

An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A pipelle should be used to obtain the specimen. A second biopsy is to be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). The biopsies will be read centrally.

6.7.1.4. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.7.1.5). To maintain blinding, concentrations of these hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.7.1.5. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping procedures are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.7.1.6. Patient Diary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. Patients will complete daily eDiaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will be reviewed by the investigator to identify any potential adverse events.

Patients will also receive a paper diary to enter information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit.

6.7.1.7. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 3). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the randomized treatment period. Patients will complete the MIQ at each visit at the site before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.8. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). Patients will complete the UFS-QoL questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.9. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale (EQ-5D) is a standardized instrument for use as a measure of health outcomes (see Appendix 5). Mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

6.7.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued,

6.7.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one sample of blood will be collected and stored for future pharmacogenomic analyses. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.7.2. Safety-Related Procedures

6.7.2.1. Weight, Height, Waist Circumference, and Body Mass Index

Patients should have weight and height measured while wearing indoor clothing and with shoes removed. Waist circumference should be measured with a measuring tape wrapped around the narrowest portion of the patient's mid-section.

6.7.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.7.2.3. Physical and Gynecologic Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. Visual acuity will be checked at the beginning and end of the study by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for women without an available test result from within 6 months prior to the Screening 1 visit and submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

6.7.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory. The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Creatinine kinase Hemoglobin A1c Creatine Kinase Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase	White Blood Cell (WBC) Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and Clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine Microscopy
	Lipids	**Pregnancy**
	Total Cholesterol Low Density Lipoprotein High Density Lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)
Hormones	**Serology**	**Iron Studies**
Thyroid-Stimulating Hormone Intact Parathyroid Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Vitamin D [25(OH)D]	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody	Iron Ferritin

A separate sample will be collected at the Day 1 visit in all patients and will be banked for hepatitis serology (Table 6-1) in all patients. The samples will be analyzed, if requested, by the medical monitor for evaluation of abnormal liver tests during the study.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, serology, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory or laboratories used.

6.7.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.7.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient). Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual subject will be monitored by a central radiology laboratory over the course of the study. Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the sties assessed during the study. In this case, repeat scan may be required for confirmation of the results, and it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.

Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of blood collected for pharmacogenomics testing (see Section 6.7.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her

sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), ECGs, bone mineral density assessments, endometrial biopsy results, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are 'intermittent'. All other events are 'continuous'. Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted, however, study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events which jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local Institutional Review Board (IRB) or Institutional Ethics Committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's eDiary entries and answers to the UFS-QoL will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Study procedure-related adverse events will be collected from the signing of the informed consent form.

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit approximately 30 days after the last dose of study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

With the exception of adverse events that are considered related to study screening procedures, (which are to be recorded as adverse events), events occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized treatment period or the Follow-up visit should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet SAE criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the International Normalized Ratio (INR) > 1.5; or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
   - Alcoholic hepatitis
   - Nonalcoholic steatohepatitis
   - Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a Safety Reporting Form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Serious Adverse Event report form and is as follows:

Send completed Safety Report Forms to PRA Safety & Risk Management:

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
North/South American sites:	PPD	PPD or PPD
Europe, Asia, Pacific and Africa sites:	PPD	PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest (AECI) reporting, please call:

- North/South America: PPD or PPD
- Europe, Asia, Pacific, and Africa: PPD

The initial report should include:

- Study number (MVT-601-3002)
- Site address and number
- Investigator name
- Patient ID number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity)
- Causal relationship to the study drug

If the patient died, the report should include the cause of death as the event term (with death as outcome) and whether or not the event leading to death was related to study drug treatment, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (ie, more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy reporting forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.7.2 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, electrocardiograms and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine fibroids. Low-dose hormonal add-back therapy with estradiol and norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (QTc prolongation), hepatic enzyme increases, PLD, reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, osteopenia, metabolic bone disease, and prior medical therapy for low bone mineral density.	Bone mineral density will be monitored at the Baseline Day 1, Week 12, and End of Treatment visits and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-gp inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec.	12-lead ECG at Baseline Day 1, Week 12 and End of Treatment visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal LFTs are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal LFTs (AST or ALT > 3 x ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be checked at the beginning and end of the study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	Clinical chemistries assessing LFTs, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% across primary and secondary endpoint testing will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL.

Statistical analyses for all efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations. The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;

- Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method;
- Time to amenorrhea as measured by the by the alkaline hematin method;
- Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities;
- Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;
- Change from Baseline to Week 24 in uterine volume; and
- Change from Baseline to Week 24 in uterine fibroid volume.

The analysis methods used for the primary endpoint will be applied to the analyses of the secondary endpoints of proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment compared between relugolix Group B and placebo Group C, the proportion of patients with amenorrhea over the last 35 days, the proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of at least 1 g/dL at Week 24 and the proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume and time to amenorrhea, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions and stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline. The between treatment comparisons will be performed using model derived least squares means with treatment, stratification factors, baseline result accounted for in the model.

Baseline Numerical Rating Scale score is defined as the average Numerical Rating Scale score from the 35 days of data collected prior to the date of first dose of study drug after randomization. The Numerical Rating Scale score during the final study month is the average Numerical Rating Scale score during the last 35 days on treatment.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment group as treated. The treatment emergent period will be defined as the period of time from the first dose date of study drug through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 12.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each parameter.

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. ECGs will also be read centrally. The distributions of corrected QT interval will be summarized at each visit. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for average of L1-L4, total hip, and femoral neck. All data will be listed and summarized by visit. The change, percent change from Baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

All data will be listed and summarized by visit. The change, percent change from baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by treatment arm.

The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar, total hip, or femoral neck) will be estimated with 95% confidence intervals by treatment group. Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.5. Pharmacokinetic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed:

- Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively;
- Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational

new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the IB, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the IB, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;

- Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
- Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
- Concomitant medication (including start and end date); and
- Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and

placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publically Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 90 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 120 days in order to obtain patent protection if deemed necessary.

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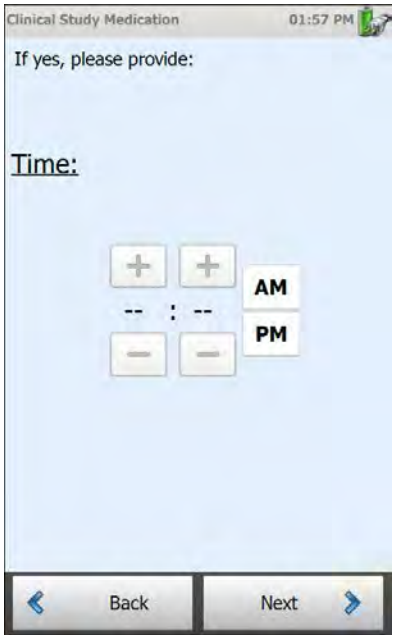
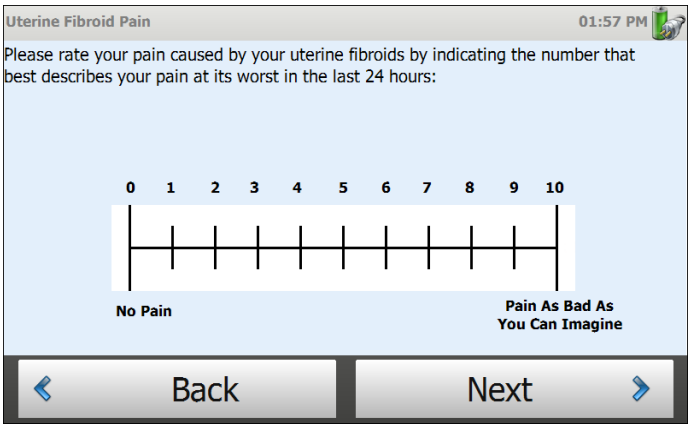
APPENDICES

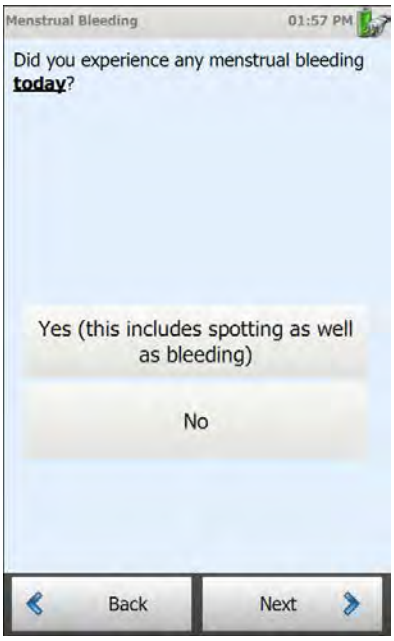
Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

Appendix 2. Daily eDiary

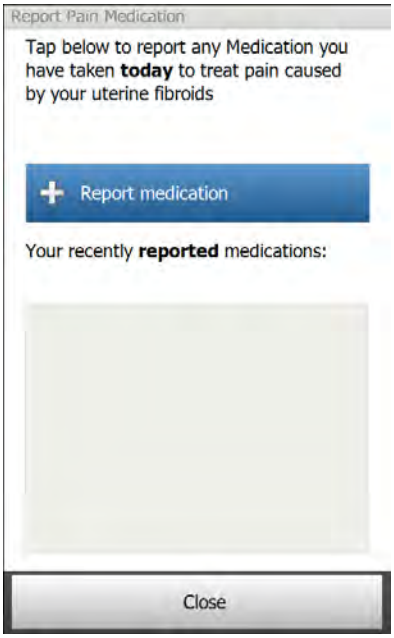


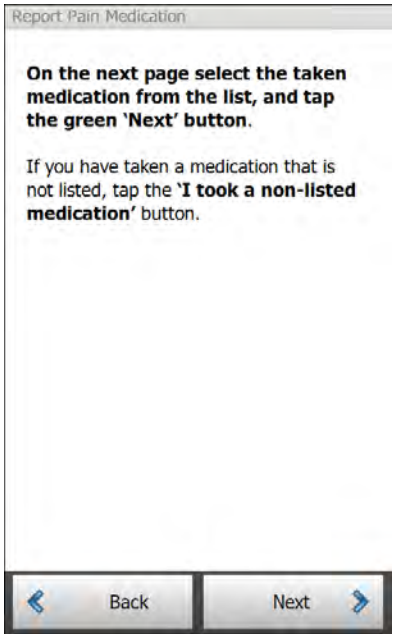



Menstrual Bleeding
01:57 PM
Did you experience any menstrual bleeding **today**?
Yes (this includes spotting as well as bleeding)
No
Back
Next

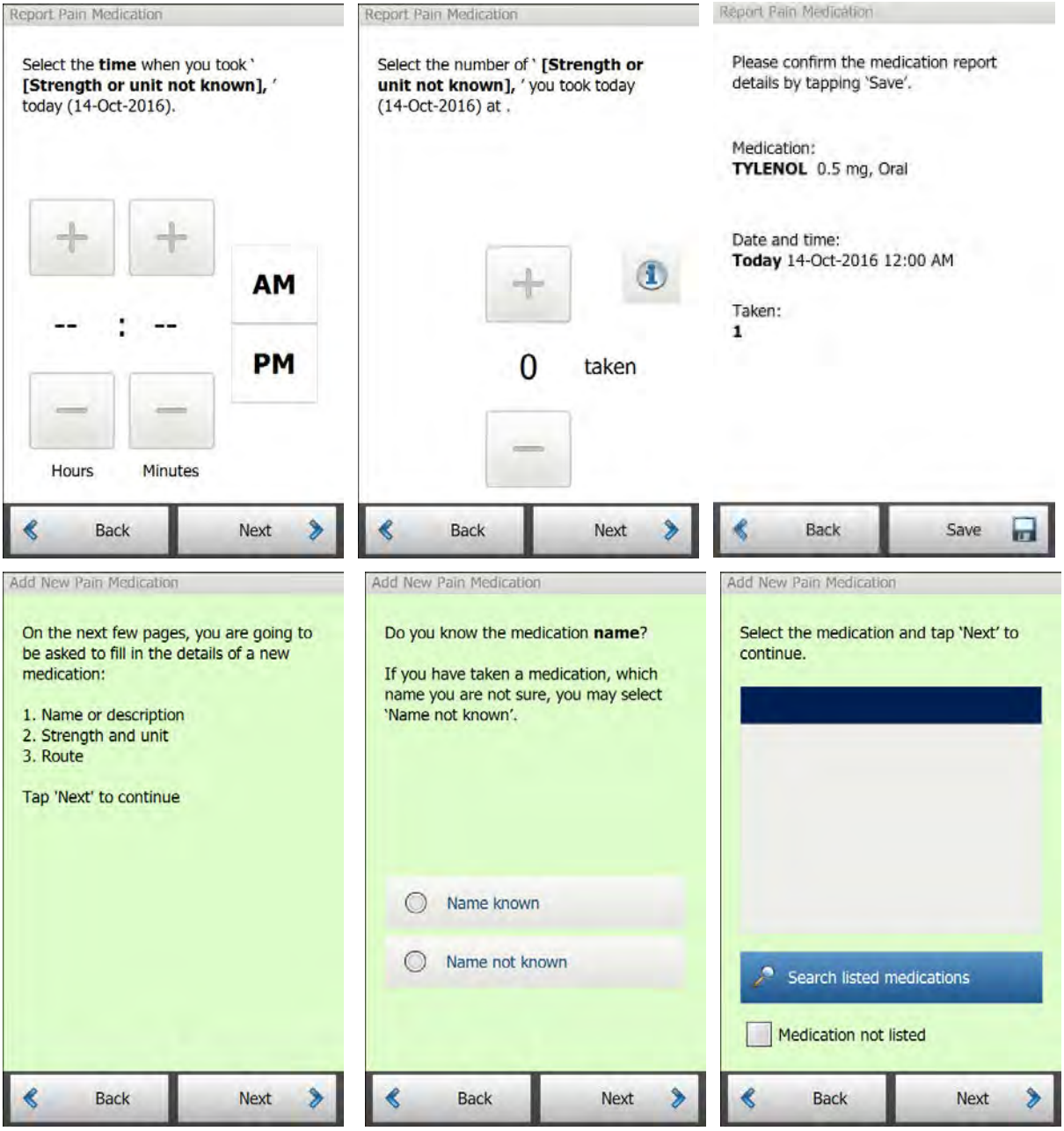

Menstrual Bleeding
01:57 PM
Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?
Yes
No
Back
Next


Use of Pain Medication
01:57 PM
Did you take any medication **today** to treat pain caused by your uterine fibroids?
Yes
No
Back
Next


Report Pain Medication
Tap below to report any Medication you have taken **today** to treat pain caused by your uterine fibroids
Report medication
Your recently **reported** medications:
Close


Report Pain Medication
On the next page select the taken medication from the list, and tap the green 'Next' button.
If you have taken a medication that is not listed, tap the **'I took a non-listed medication'** button.
Back
Next


Report Pain Medication
Select the taken **medication** from the list and tap the green **'Next'** button.
I took a non-listed medication
Back
Next

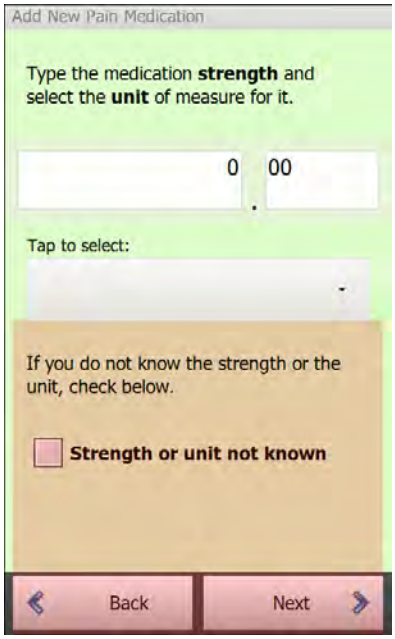

Report Pain Medication
Select the time when you took ' [Strength or unit not known], ' today (14-Oct-2016).
AM
PM
-- : --
Hours
Minutes
Back
Next
Report Pain Medication
Select the number of ' [Strength or unit not known], ' you took today (14-Oct-2016) at .
0 taken
Back
Next
Report Pain Medication
Please confirm the medication report details by tapping 'Save'.
Medication:
TYLENOL 0.5 mg, Oral
Date and time:
Today 14-Oct-2016 12:00 AM
Taken:
1
Back
Save
Add New Pain Medication
On the next few pages, you are going to be asked to fill in the details of a new medication:
1. Name or description
2. Strength and unit
3. Route
Tap 'Next' to continue
Back
Next
Add New Pain Medication
Do you know the medication name?
If you have taken a medication, which name you are not sure, you may select 'Name not known'.
Name known
Name not known
Back
Next
Add New Pain Medication
Select the medication and tap 'Next' to continue.
Search listed medications
Medication not listed
Back
Next

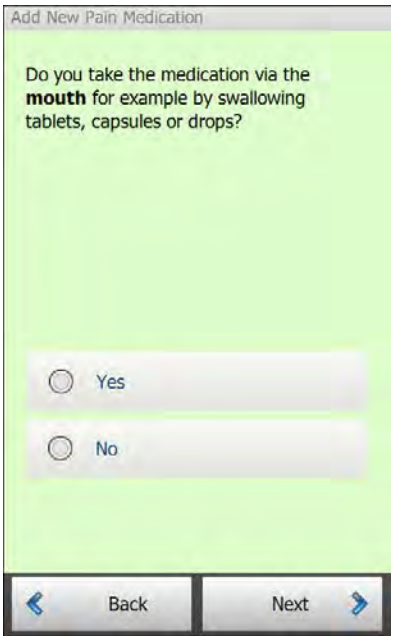

Add New Pain Medication
Enter the **first few** characters of the medication and tap 'Search'.
Tap to type:
(First characters)
Search
View all medications
Back


Add New Pain Medication
Select the medication and tap 'Next' to continue.
Medication not listed
Back
Next

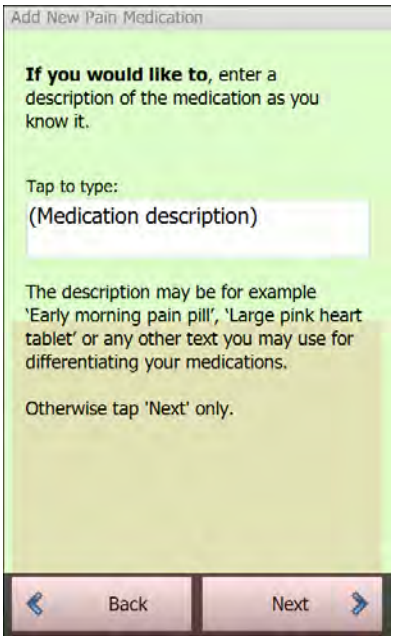

Add New Pain Medication
Please type the **name** of the medication **without** strength details.
Tap to type:
(Medication name)
Next
Back


Add New Pain Medication
Enter a description of the medication as you **know it**.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for identifying your medications.
Back
Next

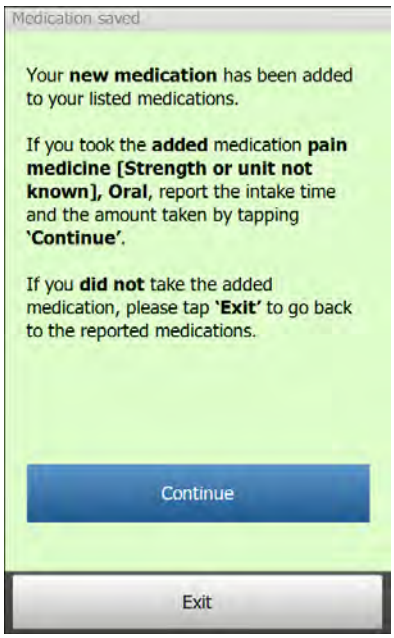

Add New Pain Medication
Type the medication **strength** and select the **unit** of measure for it.
0
00
Tap to select:
If you do not know the strength or the unit, check below.
Strength or unit not known
Back
Next


Add New Pain Medication
Do you take the medication via the **mouth** for example by swallowing tablets, capsules or drops?
Yes
No
Back
Next


Add New Pain Medication
Select the **route** for the medication:
Back
Next


Add New Pain Medication
If you would like to, enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for differentiating your medications.
Otherwise tap 'Next' only.
Back
Next


Add New Pain Medication
Please confirm the medication details by tapping **'Save'.**
Back
Save


Medication saved
Your **new medication** has been added to your listed medications.
If you took the **added** medication **pain medicine [Strength or unit not known], Oral**, report the intake time and the amount taken by tapping **'Continue'**.
If you **did not** take the added medication, please tap **'Exit'** to go back to the reported medications.
Continue
Exit

Appendix 3. Menorrhagia Impact Questionnaire

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

Pt. Initials: _____ **Pt. ID:** _____

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐	☐	☐	☐	☐
10. Made you anxious about traveling?	☐	☐	☐	☐	☐
11. Interfered with your physical activities?	☐	☐	☐	☐	☐
12. Caused you to feel tired or worn out?	☐	☐	☐	☐	☐
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐	☐	☐	☐	☐
14. Made you feel as if you are not in control of your life?	☐	☐	☐	☐	☐
15. Made you concerned about soiling underclothes?	☐	☐	☐	☐	☐
16. Made you feel less productive?	☐	☐	☐	☐	☐
17. Caused you to feel drowsy or sleepy during the day?	☐	☐	☐	☐	☐
18. Made you feel self-conscious of weight gain?	☐	☐	☐	☐	☐
19. Made you feel that it was difficult to carry out your usual activities?	☐	☐	☐	☐	☐
20. Interfered with your social activities?	☐	☐	☐	☐	☐
21. Made you feel conscious about the size and appearance of your stomach?	☐	☐	☐	☐	☐
22. Made you concerned about soiling bed linen?	☐	☐	☐	☐	☐

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel wiped out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Diminished your sexual desire?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 5. European Quality of Life Five-Dimension Five-Level Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

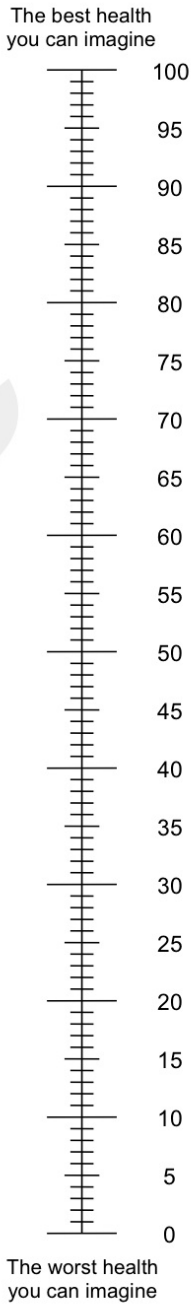
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6. Assessment of Abnormal Liver Function Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with low-dose estradiol and norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Appendix Table 1[a]; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • CBC with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.; • Serology for celiac disease; • Appropriate liver imaging; • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-005113-50 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 10-FEB-2017 Amendment 2: 25-SEP-2017

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-3002

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

25-Sep-2017
Date

25-Sep-2017
Date

25-Sept-2017
Date

25-Sep-2017
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menorrhagia Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart
PD	Pharmacodynamics
PGA	Patient Global Assessment

Term	Explanation
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QOL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3002
Location	Multinational, including North and South America, South Africa, and Europe
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	<u>Primary Efficacy Objective</u> • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. <u>Secondary Efficacy Objectives</u> • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient Global Assessment (PGA) for function and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks; • To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.
	Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures (EQ-5D-5L).

Study Design

This study is an international phase 3, randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal ultrasound (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during 1 cycle during the screening period. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during Screening must be treated with oral or parenteral iron replacement therapy. Between the

Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. Another transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken on the day immediately before to the Week 24 visit.

Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).

Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at

least one of the following criteria:

a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or

b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone;

5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use contraception during the study and for 30 days following the last dose of study drug. Specifically agrees to use non-hormonal contraception, as described in Section 4.7 consistently during the Screening period and the Randomized Treatment Period and either nonhormonal or oral contraceptives after return of menses following treatment discontinuation. However, the patient is not required to use specified non-hormonal contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described in Section 4.7;
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or < 2 cm are eligible;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study.

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);

2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline

Day 1 visit);

b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);
e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the Screening visit or Baseline Day 1 ECG;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on 2 repeat measures at least 15 minutes apart at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening or Baseline Day 1 ECG electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
    d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic

syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted; 17. Is currently pregnant or lactating, or intends to become pregnant during the study period through 1 month after the last dose of study drug or intends to donate ova during the study period or within 2 months after the last dose of study drug; 18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary window periods for these medications are also described therein); 19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form); 21. Has participated in a previous clinical study that included the use of relugolix; 22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling); 23. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor; 24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.	
Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color.

Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. <u>Primary Efficacy Endpoint</u> • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11; • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.

	Safety Endpoints • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations (Cτ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.
	Exploratory Endpoint • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of 260 (130

patients in each of the relugolix and placebo arms) will provide > 99% power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3002

	SCREENING PERIOD[a]				**RANDOMIZED TREATMENT PERIOD**								**SAFETY FOLLOW-UP**
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)		Within 5 (+2) days after completion of Screening 1 menses	Within ≤ 15 days after Screening 2 visit	Within 5 (+2) days after completion of 2nd Screening menses	Within 7 days of the start of menses	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**-10/+20**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X[e]	X
Waist Circumference					X								
Height	X												
Weight	X				X						X	X[e]	X
Temperature	X				X						X	X[e]	X
Adverse Event Collection[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity[h]					X						X	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD								SAFETY FOLLOW-UP
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Complete Physical excluding GYN Examination	X				X						X		
GYN Examination with Pap Test, if applicable	X[i]												
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X[e]	X
12-Lead Electrocardiogram			X		X			X			X	X[e]	X
Clinical Laboratory Tests[j]	X	X			X[k]	X	X	X	X	X	X[l]	X[e]	X
PK Sample[m]					X	X		X			X	X[e]	
PD Sample[n]					X	X		X			X	X[e]	X
Daily Study Drug Administration					X (Day 1 through day *immediately prior* to Week 24/Early Termination visit)							X[e]	
Administer Dose of Study Drug in Clinic					X	X	X	X	X	X		X[e]	
PGx Sample[o]					X							X[e]	
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X	X[e]	X
Urinalysis	X				X						X	X[e]	
Mammogram[p]	schedule	X											
Transvaginal Ultrasound (with or without Transabdominal Ultrasound)[q]	X										X[s]	X[e]	
Endometrial Biopsy[r]	X										X[s, w]	X[e]	
Bone Densitometry[t]	schedule	X						X			X[s, x]	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD								SAFETY FOLLOW-UP
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Un-scheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Randomization					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X		X[e]	
Dispense Study Treatment					X	X	X	X	X	X		X[e]	
Patient paper diary/ eDiary[u]	X	X	X	X	X	X	X	X	X	X	X	X[e]	
Feminine Product Collection and Venous Blood Sample[v]		X		X		X	X	X	X	X	X	X[e]	
MIQ					X	X	X	X	X	X	X	X[e]	
UFS-QOL					X			X			X	X[e]	
EQ-5D-5L					X						X	X[e]	
PGA for function[y]					X	X	X	X	X	X	X	X[e]	
PGA for symptoms[y]					X	X	X	X	X	X	X	X[e]	
Treatment Compliance and Study Drug Accountability[z]						X	X	X	X	X	X	X[e]	
Status of Menstruation Recovery													X

Notes:
Abbreviations: DXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; GYN, gynecology; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGA, Patient Global Assessment; PGx, pharmacogenomics; PK, pharmacokinetics; UFS-QOL, Uterine Fibroid Symptom and Health-Related Quality of Life.
For patients who are re-screening, please see Section 6.2.6 for abbreviated screening procedures.

a. The screening period should be initiated after the informed consent form is signed and any exclusionary windows for prohibited medications has been confirmed.
b. Visit to occur within 5 (+2) days of the completion of menses. Visit 4 should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.

c. Visit to occur within ≤ 15 days after Screening 2 visit; eDiary dispensation must occur at least 7 days prior to Baseline Day 1. The alkaline hematin menstrual blood loss collection may be repeated once at the discretion of the investigator if one menstrual cycle does not meet menstrual blood loss criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. The following procedures must be completed prior to randomization: urine pregnancy, vital signs, waist circumference, weight, temperature, complete physical examination, visual acuity assessment,12-lead ECG, and review of eligibility criteria. Collect clinical laboratory sample, PK sample, pharmacodynamic sample, and urinalysis prior to first dose of study drug. Whenever possible, complete MIQ, UFS-QOL, PGA for symptoms and PGA for function, and EQ-5D-5L prior to the first dose of study drug.
e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit. The last dose of study drug in the Randomized Treatment Period will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit is defined as the last day on which a Week 24 visit procedure is conducted.
f. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003) and/or terminate early from the study, a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~30 days after an Early Termination visit).
g. Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure) through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first.
h. Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100; continue as far as the patient can go per the testing instructions. See Study Reference Manual for additional instructions on visual acuity testing and see Section 6.8.2.8 for overall guidance including follow-up.
i. Papanicolaou test must be conducted for women without a test result within 2 years prior to the Screening 1 visit. The specimen should be submitted to the central laboratory during screening. Another test should be performed for inadequate or false-positive results and be submitted to the central laboratory.
j. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests. In addition to clinical chemistries and a complete blood count, include thyroid-stimulating hormone at Screening 1. Screening laboratory tests may be repeated during the screening period once, if necessary, at the investigator's discretion. Additional re-testing requires the approval of the medical monitor. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.
k. At the Baseline Day 1 visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, prolactin, Vitamin D, and hemoglobin A1c. An additional sample will be collected at this visit in all patients and stored for possible future testing for presence of hepatitis A, B, and C if required per request from medical monitor to assess etiology of liver test abnormalities.
l. At the Week 24 visit or Early Termination visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.
m. Pharmacokinetics samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics

sample collections are complete (Study drug is not administered at Week 24 Visit; for patients proceeding into the extension study, refer to protocol for study MVT-601-3003).

n. Pharmacodynamic samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Early Termination and Follow Up visits). Study drug is not administered at the Week 24 Visit for patients proceeding into the extension study (refer to protocol for study MVT-601-3003).
o. Pharmacogenomics sample (unless precluded by local law or regulations): a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive)
p. Patients ≥ 39 years of age at the time of the anticipated Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period; if not, schedule at the Screening 1 visit.
q. Transvaginal ultrasound with or without transabdominal ultrasound must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm. Results must be submitted to and uterine fibroid criteria confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is required. See inclusion criterion #5 and exclusion criterion #1 for guidance as to when to perform a transabdominal ultrasound and saline or gel contrast. If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24.
r. Obtain sample with an endometrial suction curette (eg, Pipelle®). Endometrial biopsy is performed at Screening 1 visit in all patients (and Week 24 Visit only if indicated [endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound]) and submitted to the central laboratory. See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis.
s. Procedure not required at the Early Termination Visit in patients whose last dose of study drug was during Week 6 or earlier. The procedure may be done if it will aid in the evaluation of an ongoing adverse event.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results will be available prior to randomization. Schedule the test at or shortly after the Screening 1 visit. Bone densitometry should be completed prior to the Screening 3 visit and as early as possible to ensure results are available prior to randomization.
u. Patient paper diary: Patients enter diary information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit. Patient eDiary: Ensure that eDiary data collection begins at least 7 days prior to Day 1. Patients enter eDiary information on a daily basis for their compliance with study treatment starting at Baseline/Day 1, menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening 3 visit through Week 24 or Early Termination.
v. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.
w. Patients not proceeding to the extension study who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will be followed and will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination visit (see Section 6.7). The repeat biopsy will be submitted to the central laboratory.
x. Schedule DXA as early as possible within the Week 24/Early Termination visit window. Patients not proceeding to the extension study who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo another DXA scan at 6 (± 1) months after the Week 24/Early Termination visit scan to evaluate recovery and will be contacted about medications and conditions

(eg, pregnancy) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.

y. Patient will enter responses in a paper questionnaire at the site.
z. The patient should be asked to bring all study drug to the clinic at each visit. Please refer to Section 5.8.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which

are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotropin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies (including 1 in women with uterine fibroids and 1 in women with endometriosis) have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least 1 dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations of estradiol in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

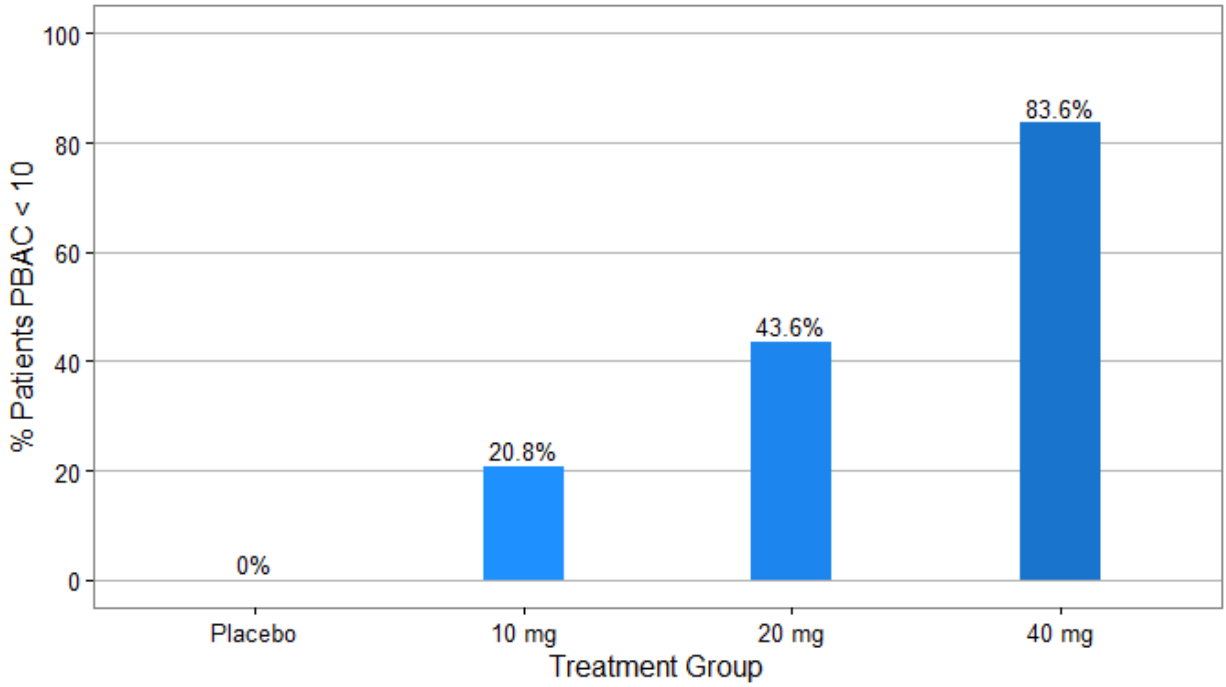
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 19%. The exposure of relugolix is increased by inhibitors

of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 final analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤ 50 ng/dL) and maintained these levels through at least 24 weeks. These 24-week data were comparable to testosterone levels achieved by leuprolide 22.5 mg administered by injection every 3 months. Study C27003 also demonstrated rapid and sustained suppression of testosterone levels by relugolix for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. Adverse drug reactions associated with relugolix in women with uterine fibroids or endometriosis include hot flush, headache, hyperhidrosis and bone density decreased. Adverse drug reactions associated with relugolix in men with prostate cancer include hot flush, fatigue, arthralgia, nausea, weight increased, gynecomastia and night sweats.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
<u>Primary Efficacy</u>	
• To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
<u>Secondary Efficacy</u>	
• To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of uterine fibroids on symptoms, activities and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient Global Assessment (PGA) for function	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin

Objective(s)	Endpoint(s)
and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.	below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11; • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of	• Treatment-emergent adverse events, change

Objective(s)	Endpoint(s)
relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks; • To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids.	in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.
<u>Pharmacokinetic and Pharmacodynamic</u>	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.
<u>Exploratory</u>	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures (EQ-5D-5L).	• Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3, randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal ultrasound (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during 1 cycle during the screening period. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. Another transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken on the immediate day prior to the Week 24 visit.

Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits are provided in Figure 4-2.

Figure 4-1 MVT-601-3002 Study Schematic

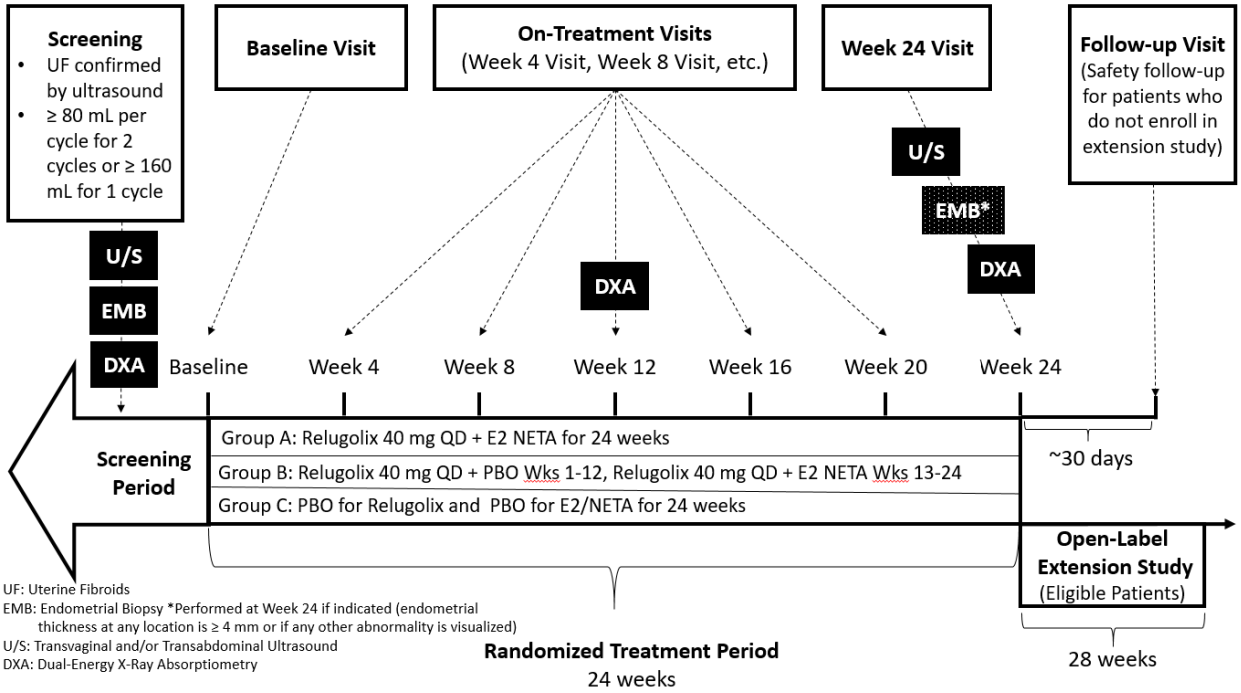


Figure 4-2 Schematic of MVT-601-3002 Screening Visit Scenarios

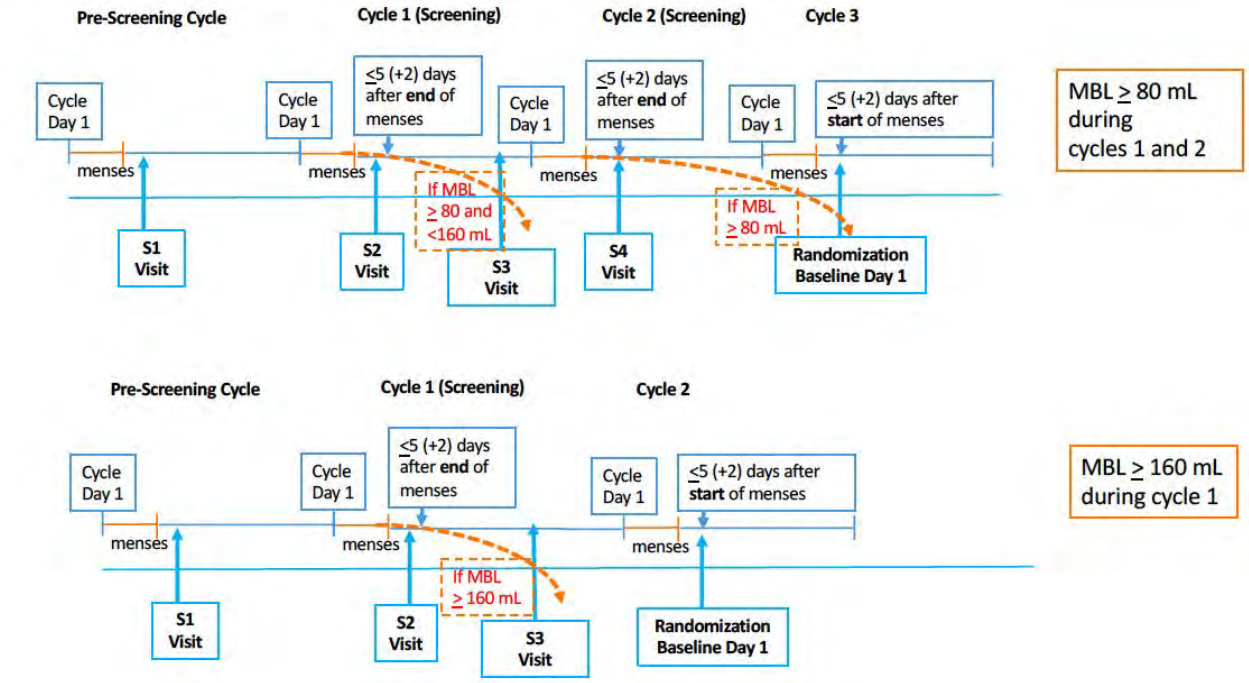


Figure 4-2

Screening visit 1 may be conducted at any time during the pre-screening cycle.

Top scenario:

- Eligibility is based on 2 consecutive screening cycles, each with ≥ 80 mL of menstrual blood loss assessed by the alkaline hematin method where the first screening cycle menstrual blood loss is also < 160 mL.

Bottom scenario:

- Eligibility is based on first screening cycle with ≥ 160 mL menstrual blood loss assessed by the alkaline hematin method.

Additional Scenarios (not depicted):

- Patients whose first screening cycle menstrual blood loss is < 80 mL and whose second screening menstrual blood loss is ≥ 80 mL but < 160 mL may collect menstrual blood loss during a third screening cycle if the first collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is ≥ 80 mL but < 160 mL and whose second screening menstrual blood loss is < 80 mL may collect menstrual blood loss during a third screening cycle if the second collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is < 80 mL may collect menstrual blood loss during a second cycle if the first collection was believed to be inadequate in a highly motivated patient. If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule, and the patient does not need to collect menstrual blood loss for another cycle.

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This study will focus on the primary objective of demonstrating a reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study is designed to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An extension study is planned to provide additional safety and efficacy data through 48 weeks.

Women with uterine fibroids and heavy menstrual blood loss by the alkaline hematin method of ≥ 80 mL/cycle for two cycles or ≥ 160 mL in one cycle during screening will be enrolled in this study. Randomization will be 1:1:1. Placebo was selected as the appropriate control for the study because there is no standard of care medical therapy for the long-term treatment of women with uterine fibroids and heavy menstrual bleeding. Commonly-used treatment options range from combined oral contraceptive pills, which are not effective in many cases, levonorgestrel-containing intrauterine devices, and leuprolide therapy indicated for 3 months in the preoperative setting.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. This dose was selected for evaluation in phase 2 clinical studies based upon phase 1 data demonstrating similar estradiol and progesterone suppression in women treated with single doses of relugolix 40 mg or 80 mg, and data demonstrating that premenopausal women treated with multiple doses of 40 mg once daily relugolix over 14 days had estradiol levels suppressed to a median value of 3.68 pg/mL.

Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, as described above, a phase 2 study of doses of relugolix 10, 20 and 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not

provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 48 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 48 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 1992; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the US as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate has demonstrated that this dose of add-back therapy maintains serum estradiol in the 25-50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy and is not included as a control arm as it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in a well-designed

large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study will primarily assess the efficacy and safety of relugolix 40 mg co-administered with a low-dose of estradiol and norethindrone acetate compared with placebo at 24 weeks to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes. An additional arm with monotherapy relugolix administered for 12 weeks followed by 12 weeks of relugolix co-administered with low-dose hormonal add-back therapy is included to provide data on the requirement for hormonal therapy to mitigate the adverse relugolix side effects of bone mineral density loss and hot flushes.

All eligible women who complete the 24-week study will be offered the opportunity to enroll in an open-label extension study to obtain long-term safety and efficacy data over an additional 28 weeks of treatment, providing approximately 1 year of safety data on the women originally randomized to relugolix.

4.3. Selection of Study Population

The study population will include approximately 390 premenopausal women aged 18 to 50 years with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for randomization and enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Baseline Day 1 visit, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;

4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

    Note 1: Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

    Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone.
5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use contraception during the study and for 30 days following the last dose of study drug. Specifically agrees to use non-hormonal contraception, as described in Section 4.7 consistently during the Screening period and the Randomized Treatment Period and either nonhormonal or oral contraceptives after return of menses following treatment discontinuation. However, the patient is not required to use specified non-hormonal contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described in Section 4.7;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or < 2 cm are eligible;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;

10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
    d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);
    e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the Screening visit or Baseline Day 1 ECG;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on 2 repeat measures at least 15 minutes apart at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
    d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis,

psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;

17. Is currently pregnant or lactating, or intends to become pregnant during the study period through 1 month after the last dose of study drug or intends to donate ova during the study period or within 2 months after the last dose of study drug;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor;
24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

4.5. Method of Assigning Patients to Treatment Group and Patient ID Number

After a patient is screened, the investigator determines that the patient is eligible for enrollment, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Web Response System (IWRS) during the patient's Baseline Day 1 visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IWRS will also assign the Patient Identification Number (Randomization Number).

4.6. Removal of Patients from Therapy

Completion of the Week 24 defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements. This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; missing multiple study visits; and persistent (> 2 consecutive months) with < 50% of the required number of days of eDiary completion;
- Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain

contact with the patient. The site should attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug, unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of contraception for those for whom one of the above methods do not apply are:

- Condom (male or female condom) with or without spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 2 months following the last dose of study drug.

A patient may start hormonal contraception 4 weeks after her last study dose of study drug provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including just prior to receiving first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

Each patient will be instructed to take one tablet and one capsule per day. The last dose of study drug will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, and color. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

Table 5-1 Description of MVT-601-3002 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An Swedish orange, over-encapsulated round film-coated white tablet with placebo back-fill material	A Swedish orange capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients.

Placebo to match relugolix is a pink tablet using common excipients.

The fixed-dose combination tablet of estradiol 1.0 mg and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3002 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with estradiol / 0.5 mg norethindrone acetate placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule for 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss measured by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state (other than water, tea, or coffee) in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

On selected clinic days, study drug will be administered in the clinic (refer to Sections 1.1 and Section 6.3) or the visits during which patients take study drug in the clinic rather than at home)

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 25°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix, the estradiol/norethindrone acetate combination, relugolix placebo, and the estradiol/norethindrone acetate placebo to be distributed will meet all applicable requirements of the US FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Relugolix 40 mg and relugolix placebo will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate or estradiol/norethindrone acetate placebo.

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding by the investigator for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. The decision to unblind a patient's treatment assignment in an emergency situation resides with the investigator who has direct access to unblind a patient's individual study treatment; however, the investigator should attempt to contact the medical monitor or appropriate study personnel to discuss options before unblinding the patient's treatment assignment unless the urgency of the medical situation precludes this. If unblinding by the investigator occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient. Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment.

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused and used study drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment it may be appropriate to withdraw the patient from the study (see Section 4.6). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zolendronic acid	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone **Note**: All other anticonvulsants are allowed	1 month
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	2 months (6 months for depot subcutaneous or intramusclar injections)
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	2 months (6 months for depot subcutaneous or intramusclar injections)
Hormonal Contraceptives, contraceptive patches and vaginal rings	combined or progestin only Nuva Ring	1 month for patients reporting a typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	1 week

Drug Class	Examples	Window/Comments
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	No prior use if used for reduced bone mineral density Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin clopidogrel tranexamic acid vitamin k preparations factor Xa inhibitors	1 month
Glucocorticoids	prednisolone or prednisone dexamethasone	No window Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration ($\leq$ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir	2 weeks Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Drug Class	Examples	Window/Comments
Moderate and Strong P-glycoprotein Inhibitors	amiodarone atazanavir[f] azithromycin[a] captopril[b] carvedilol[g] clarithromycin[a] cobicistat[f] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	2 weeks (6 months for amiodarone) Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone
a. Roxithromycin is allowed
b. All other angiotensin converting enzyme inhibitors are allowed
c. Tacrolimus is allowed
d. Amlodipine and nifedipine are allowed
e. Fluconazole is allowed
f. Integrase inhibitors are allowed
g. Metoprolol and atenolol are permitted

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

From the Screening 1 visit to the Week 24 (or Early Termination) visit, the recommended analgesics for uterine-fibroid associated pain are as follows:

- First-line: ibuprofen
- Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
- Third-line: opioid or opioid-acetaminophen combination
- Fourth-line: investigator discretion

The purpose of these recommendations is to standardize, to the extent possible, analgesic medication use to facilitate the effects on the secondary endpoint regarding of uterine-fibroid-related pain.

Patients should be instructed not to use analgesics for prophylactic purposes.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL and ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.8. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities in the study synopsis (see Section 1.1). The study is divided into three periods: screening period, randomized treatment period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study; unscheduled visits may also occur as needed to evaluate patients).

6.2. Screening Period

Patients should have a diagnosis of uterine fibroids and a history of heavy menstrual bleeding with or without associated pain on a background of generally regular menses (ie, regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next menstrual period) as reported by the patient for at least 3 months prior to the Screening 1 visit.

The screening period consists of the Screening 1, 2, 3, and 4 visits.

See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening. The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.

6.2.1. Screening 1 Visit

The Screening 1 visit will be conducted following the signing of the informed consent form and may occur at any time during the menstrual cycle. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications, study procedure-related adverse events and any serious adverse events. In addition, vital signs, height, weight, temperature, a complete physical examination, visual acuity assessment, gynecology examination, ultrasound, endometrial biopsy, Papanicolaou test (if needed), clinical laboratory tests, urinalysis, and a urine pregnancy test will be done. Feminine products will be dispensed with instructions to collect and return all products used during the next menses. The paper diary will also be dispensed at this visit and should be completed daily starting with this visit. The bone mineral density scan and mammogram should be scheduled at this time (or within a few days of this visit). Bone densitometry should be scheduled to be prior to the Screening 3 visit and as early as feasible to ensure results are available prior to randomization.

The order of procedures should be as follows. Patients not meeting eligibility criteria after any procedure should not undergo subsequent procedures.

- Medical history and review of prior uterine imaging studies
- Review of concomitant medications (including supplements and over the counter medications)
- Review of inclusion and exclusion criteria
- Urine pregnancy test
- Vital signs, weight, and height
- Complete physical examination and visual acuity assessment
- Ultrasound – do not proceed with additional procedures if no uterine fibroids are identified with the local/initial reading
- Gynecology examination, Papanicolaou test (if need), endometrial biopsy, clinical laboratory tests, including TSH, urinalysis
- Dispense feminine products and paper diary with instructions to begin recording starting information daily, starting on the Screening 1 visit day
- Schedule mammogram (if needed)
- Schedule bone densitometry

The ultrasound will be a transvaginal ultrasound with or without a transabdominal ultrasound (see Section 4.3 ultrasound entry criteria), performed to assess for uterine fibroids. Saline or gel contrast may be used but is not required (see Section 4.3 ultrasound entry criteria). The anatomic location and size of the fibroid disease will be estimated by the local reader. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to

randomization). The investigator, rather than the central reader, will determine if any exclusionary pathology is present. If ultrasound fails to demonstrate fibroids on the local reading, do not proceed with additional Screening visit 1 procedures.

The Papanicolaou test must be conducted for women without a test result within 2 years prior to the Screening 1 visit and the specimen is to be submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

The endometrial biopsy will be obtained with an endometrial suction curette (eg, Pipelle®) and submitted to the Central Laboratory.

The mammogram must be done in patients ≥ 39 years of age by the time of the (anticipated) Baseline Day 1 visit if there is no record (and reading) from within 6 months prior to the screening period.

If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab. Please see Section 5.10.2.2 for guidance on iron therapy.

6.2.2. Screening 2 Visit

Screening 2 visit is scheduled to occur within 5 (+2) days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine products. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine products will be dispensed for collection of menstrual blood loss during the next menses. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab. Women whose laboratory testing reveals iron-deficiency anemia as defined in the study must be started on iron therapy.

Confirm the scheduling of the bone densitometry and mammogram (if needed) and review mammogram results, if available. The mammogram must be normal (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) in order for the patient to be eligible.

Once the menstrual blood loss results from the first cycle are available, schedule Screening 3 visit as soon as feasible and within 5 (+2) days of receiving results showing that the menstrual blood loss is ≥ 80 mL

Patients will be dispensed feminine products to be gathered for the second cycle.

6.2.3. Screening 3 Visit

The patient will return for the Screening 3 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL and within ≤ 15 days after the Screening 2 visit. At the Screening 3 visit, review of inclusion and exclusion criteria will be conducted to confirm continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. At this visit, review the endometrial biopsy results and review mammogram results, if available.

Confirm that the bone densitometry scans have been submitted for central reading. The mammogram and central bone densitometry results must be available prior to randomization.

6.2.4. Screening 4 Visit

The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle. If not skipped, then the Screening 4 visit is scheduled to occur within 5 (+2) days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn for hemoglobin assessment. The patient's eDiary data collection will be reviewed. Laboratory and imaging evaluations will be reviewed to ensure eligibility for randomization.

6.2.5. Menstrual Blood Loss Repeat Collection

At the discretion of the investigator, the collection of menstrual blood loss can be repeated once during the screening period (either after the first or second screening cycle) if one menstrual cycle does not meet the heavy menstrual bleeding alkaline hematin criteria and it is thought to be due to an inadequate collection by a highly motivated patient.

6.2.6. Re-Screening

Patients who fail screening may be re-screened with approval of the medical monitor. Patients undergoing re-screening will sign a new informed consent form and issued a new screening number. For patients who begin re-screening within 10 weeks of signing the original informed consent form, transvaginal ultrasound, endometrial biopsy, and bone densitometry do not need to be repeated, if performed previously.

6.2.7. Retesting

Screening laboratory tests may be repeated once during the Screening period, if necessary, at the investigator's discretion. For laboratory-based entry criteria, the most recent value will be used to determine eligibility. Additional laboratory retesting requires the approval of the medical monitor. Retesting of other procedures (except once, as required, due to technical or logistical issues such as an inadequate sample) also require approval of the medical monitor.

6.3. Randomized Treatment Period (Baseline to Week 24)

At the Baseline Day 1 visit, patients will be randomized to one of the three study treatment arms (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the Week 24 visit. Patients will continue recording daily in their eDiary. On-treatment study visits will occur every 4 weeks through the end of Week 24. At each post-baseline visit, patients will return their feminine products for alkaline hematin testing. Safety monitoring including signs and symptoms directed physical examination, waist circumference, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12

and Week 24 visits. A repeat transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at the Week 24 visit. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). The endometrial biopsy will be read centrally. Study drug and eDiary compliance will be reviewed at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the randomized treatment period.

Sites should try to schedule patient visits during the morning, instructing patients to arrive before taking their study drug to allow for pre-dose PK/pharmacodynamic sampling on visits at which these specimens are drawn. Patients must come to the clinic in the fasted state (eg, nothing to eat or drink other than water after midnight the day before the clinic visit) for the Baseline Day 1 and Week 24/Early Termination visits.

For visits *other than* Baseline Day 1 and Week 24/Early Termination, if the clinic visit cannot be scheduled for the morning, patients may eat in the morning but should not have eaten or had anything to drink other than water, coffee, or tea for at least 2 hours prior to the clinic visit and must not eat or drink (other than water, coffee or tea) for at least 1 hour after the clinic visit. In these situations, the laboratory requisitions must indicate that the patient was not fasted for their chemistry and lipid testing.

6.4. Continuation into Extension Study

It is expected that most patients will enter the 28-week extension study (MVT-601-3003), which will be conducted under a separate protocol. Patients will provide separate informed consent to participate in the extension study during which all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate.

6.5. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 24 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 24; however, for patients whose last dose of study drug is during Week 6 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound), endometrial biopsy, and bone densitometry. These procedures may be performed, however, at the investigator's discretion, if they aid in follow-up of ongoing adverse events.

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3003), will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation. Patients who withdraw early from this study will also undergo the Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Refer to the Schedule of

Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Additional Safety Follow-Up Procedures

For patients not continuing into the extension study (MVT-601-3003), additional safety procedures are required in some circumstances as described below. These procedures will be performed during unscheduled visits.

- Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.
- Patients with endometrial biopsy findings of endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory. In addition, patients with endometrial hyperplasia with atypia will be evaluated and managed, as needed, by a gynecologist.
- Patients who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.

6.7. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, PK and pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.8. Study Procedures

6.8.1. Efficacy-Related Procedures

6.8.1.1. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.8.1.2. Transvaginal and Transabdominal Ultrasound

Transvaginal with or without transabdominal ultrasound with or without saline or gel contrast is performed for the diagnosis of uterine fibroids, to determine uterine and myoma volumes, and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Transvaginal ultrasound will be performed. Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = D1 x D2 x D3 x π / 6
Where:
D1 = the longest diameter of the myoma or uterus (unit of length: cm)
D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone or when endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.). If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24.

6.8.1.3. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.8.1.4). To maintain blinding, concentrations of these hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.8.1.4. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping procedures are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.8.1.5. Patient Diary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. Patients will complete daily eDiaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will be reviewed by the study staff.

Patients will also receive a paper diary to enter information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit.

6.8.1.6. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 3). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the randomized treatment period. With exception of Baseline Day 1 (see Section 1.1), patients will complete the MIQ at each visit at the site before other study procedures.

6.8.1.7. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL) score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). Patients will complete the UFS-QOL questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit. With the exception of Baseline Day 1 (see Section 1.1), patients will complete the UFS-QOL before other study procedures.

6.8.1.8. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale (EQ-5D-5L) is a standardized instrument for use as a measure of health outcomes (see Appendix 5). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 5-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D-5L questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit. With the exception of Baseline Day 1 (see Section 1.1), patients will complete EQ-5D-5L before other study procedures.

6.8.1.9. Patient Global Assessment for Symptoms and Patient Global Assessment for Function

These simple questions are used by the patient to qualitatively describe severity of symptoms or effects on function (PGA) (see Appendix 6) on a schedule described in the Schedule of Activities (see Section 1.1). With the exception of Baseline Day 1 (see Section 1.1), patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Section 1.1). With the exception of Baseline Day 1, patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site.

6.8.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF.

Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.

6.8.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one sample of blood will be collected and stored for future pharmacogenomic analyses, unless precluded by local law or regulations. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.8.2. Safety-Related Procedures

6.8.2.1. Weight, Height, Waist Circumference, and Body Mass Index

Patients should have weight and height measured while wearing indoor clothing and with shoes removed. Waist circumference should be measured with a measuring tape wrapped around the narrowest portion of the patient's mid-section.

6.8.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.8.2.3. Physical and Gynecologic Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for women without an available test result from within 2 years prior to the Screening 1 visit and submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

6.8.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory. The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Hemoglobin A1c Creatine Kinase Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase	White Blood Cell (WBC) Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and Clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine Microscopy
	Lipids	**Pregnancy**
	Total Cholesterol Low Density Lipoprotein High Density Lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)
Hormones	**Serology**	**Iron Studies**
Thyroid-Stimulating Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Vitamin D [25(OH)D]	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody	Iron Ferritin

A separate sample will be collected at the Day 1 visit in all patients and will be banked for hepatitis serology (Table 6-1). The samples will be analyzed, if requested, by the medical monitor for evaluation of abnormal liver tests during the study.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, serology, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally. If the hemoglobin is $\leq$ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges for the laboratory or laboratories used.

6.8.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.8.2.6. Endometrial Biopsy

An endometrial biopsy will be obtained using an endometrial suction curette (eg, Pipelle) and submitted to the central laboratory for reading. If the biopsy is inadequate for diagnosis at either Screening or at Week 24, it should be repeated and sample submitted to the central laboratory. If the second specimen is also inadequate for diagnosis at Screening, the patient is not eligible for the study. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound).

6.8.2.7. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient). The scans will be read by the central radiology laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual patient will be monitored by a central radiology laboratory over the course of the study. Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the anatomical sites assessed during the study. In this case, it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for DXA scanning will be provided in the Study Reference Manual.

Please see Section 6.6 for follow-up of patients who are not continuing into the extension study (MVT-601-3003) and whose bone mineral density has decreased by > 2% at the lumbar spine (L1-L4) or total hip at the Week 24/Early Termination visit relative to Baseline.

6.8.2.8. Visual Acuity

Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see Study Reference Manual for additional details).

Patients whose presenting visual acuity score is 90 or lower at the Baseline visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history.

Patients whose presenting visual acuity score at Week 24 /Early termination has decreased by 10 or more points from Baseline should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

6.8.3. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of blood collected for pharmacogenomics testing (see Section 6.8.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), ECGs, bone mineral density assessments, endometrial biopsy results, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).
- Events of heavy menstrual bleeding, as heavy menstrual bleeding is being quantitatively measured as an efficacy endpoint, unless the event meets seriousness criteria.

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are 'intermittent'. All other events are 'continuous'. Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events which jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local Institutional Review Board (IRB) or Institutional Ethics Committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's eDiary entries and answers to the UFS-QOL will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Study procedure-related adverse events will be collected from the signing of the informed consent form.

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit approximately 30 days after the last dose of study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

With the exception of adverse events that are considered related to study screening procedures, (which are to be recorded as adverse events), events occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).

- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized treatment period or the Follow-up visit should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet SAE criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 7.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the International Normalized Ratio (INR) > 1.5; or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
   - Alcoholic hepatitis
   - Nonalcoholic steatohepatitis
   - Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a Safety Reporting Form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Serious Adverse Event report form and is as follows:

Send completed Safety Report Forms to QuintilesIMS:

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
All Regions	PPD	PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest (AECI) reporting, please call:

- North/South America: PPD
- Regional toll-free phone and fax lines distributed separately. Please refer to Study Reference Manual.

The initial report should include:

- Study number (MVT-601-3002)
- Site address and number
- Investigator name
- Patient ID number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity)
- Causal relationship to the study drug

If the patient died, the report should include the cause of death as the event term (with death as outcome) and whether or not the event leading to death was related to study drug treatment, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the

initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (ie, more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy reporting forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.8.2 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, electrocardiograms and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine fibroids. Low-dose hormonal add-back therapy with estradiol and norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (QTc prolongation), hepatic enzyme increases, PLD, reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density.	Bone mineral density will be monitored at the Baseline Day 1, Week 12, and End of Treatment visits and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-gp inhibitors/inducers.	Collection of adverse events.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec.	12-lead ECG at Baseline Day 1, Week 12 and End of Treatment visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzyme Increase Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal LFTs are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal LFTs (AST or ALT > 3 x ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be checked at the beginning and end of the study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior	Clinical chemistries assessing LFTs, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	Monitoring and Withdrawal Criteria
estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	hypersensitivity, migraine with aura, porphyria, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% across primary and secondary endpoint testing will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL.

Statistical analyses for all efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the ITT Population who have no relevant major protocol violations, defined as a subset of all major protocol violations (details will be provided in the statistical analysis plan). The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population.

This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at

significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;
- Proportion of women who achieve amenorrhea over the last 35 days of treatment;
- Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24;
- Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain;
- Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11;
- Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20;
- Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29;
- Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity;
- Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life;
- Change in PGA for uterine fibroid related function from Baseline to Week 24;
- Change in PGA for uterine fibroid symptoms from Baseline to Week 24;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities;
- Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;
- Change from Baseline to Week 24 in uterine volume; and

- Change from Baseline to Week 24 in uterine fibroid volume.

The analysis methods used for the primary endpoint will be applied to the analyses of the secondary endpoints of proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment compared between relugolix Group B and placebo Group C, the proportion of patients with amenorrhea over the last 35 days, the proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of at least 1 g/dL at Week 24 and the proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume, time to event will be defined as weeks from randomization to first occurrence of the event as assessed by the alkaline hematin method. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions and stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, UFS-QOL score, PGA for function and symptoms, MIQ Score, Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline. The between treatment comparisons will be performed using model derived least squares means with treatment, stratification factors, baseline result accounted for in the model.

Baseline Numerical Rating Scale score is defined as the average Numerical Rating Scale score from the 35 days of data collected prior to the date of first dose of study drug after randomization. The Numerical Rating Scale score during the final study month is the average Numerical Rating Scale score during the last 35 days on treatment.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment group as treated. The treatment emergent period will be defined as the period of time from the first dose date of the randomized study drug treatment through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, or the date and time of the first dose of open-label extension (MVT-601-3003) study drug, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ

class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each parameter.

ECGs will be read centrally. The distributions of corrected QT interval will be summarized at each visit. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

Bone mineral density will be determined by the central radiology laboratory at the femoral neck, lumbar spine (L1-L4), and total hip. Values at Baseline, Week 12, and Week 24 visits will be summarized by treatment group along with the absolute and percent changes from Baseline and associated 95% confidence intervals. The number and percentage of patients meeting a bone mineral density decline of at least 7% by body area (lumbar, total hip, and femoral neck) will be presented with 95% confidence intervals by treatment group.

To support the inclusion of add-back therapy in the treatment regimen, the safety endpoint of mean percent change from Baseline in bone mineral density lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal comparison of Group A versus Group B (see details in the joint statistical analysis plan).

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by treatment arm.

9.5. Pharmacokinetic and Pharmacodynamic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoint. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoint will be assessed:

- Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Council on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed

consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the IB, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the IB, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;
   - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
   - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
   - Concomitant medication (including start and end date); and
   - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory

authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 90 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 120 days in order to obtain patent protection if deemed necessary.

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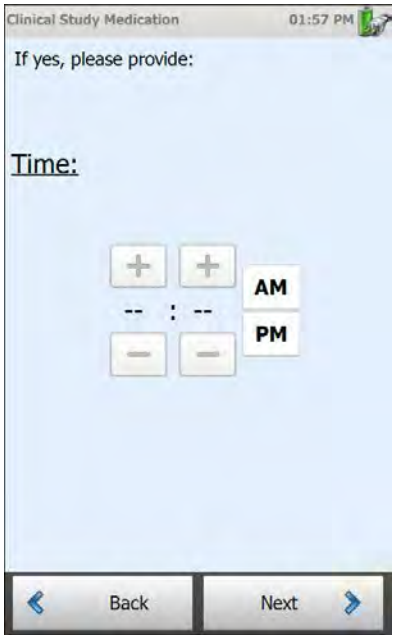
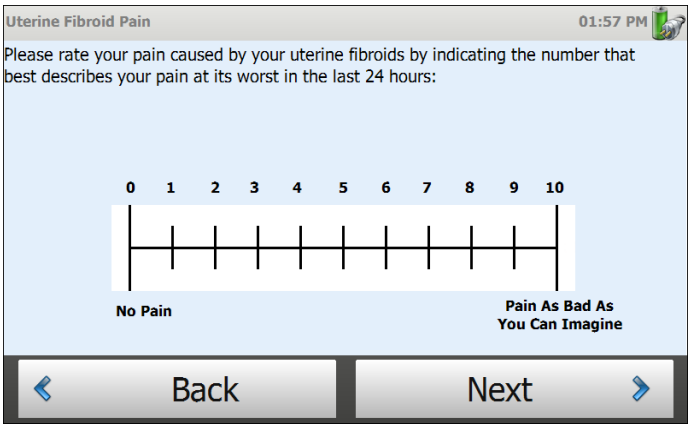
APPENDICES

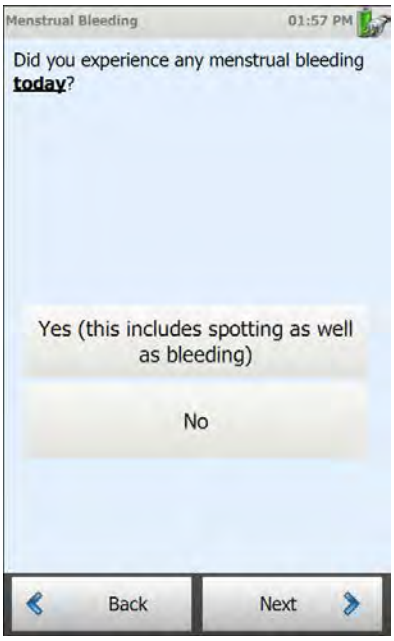
Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

Appendix 2. Daily eDiary

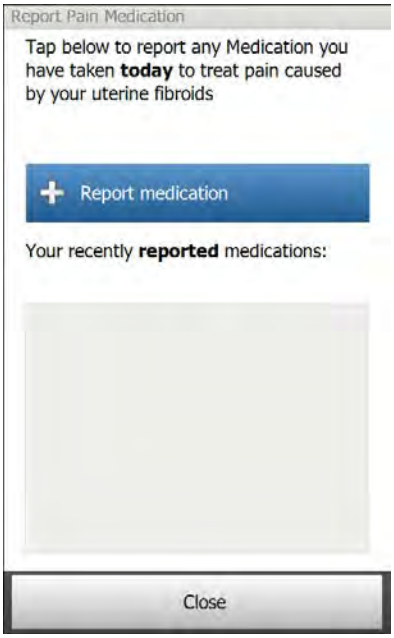


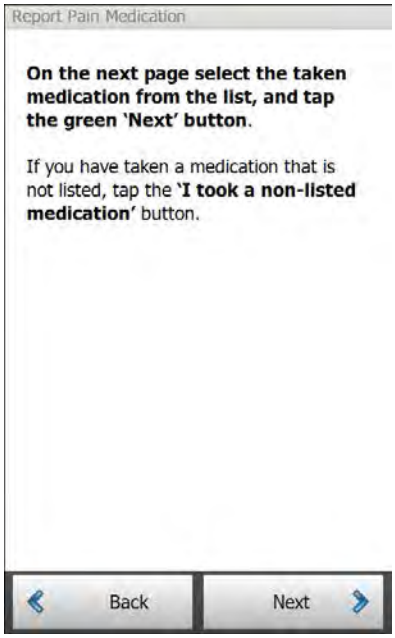



Menstrual Bleeding
01:57 PM
Did you experience any menstrual bleeding **today**?
Yes (this includes spotting as well as bleeding)
No
Back
Next

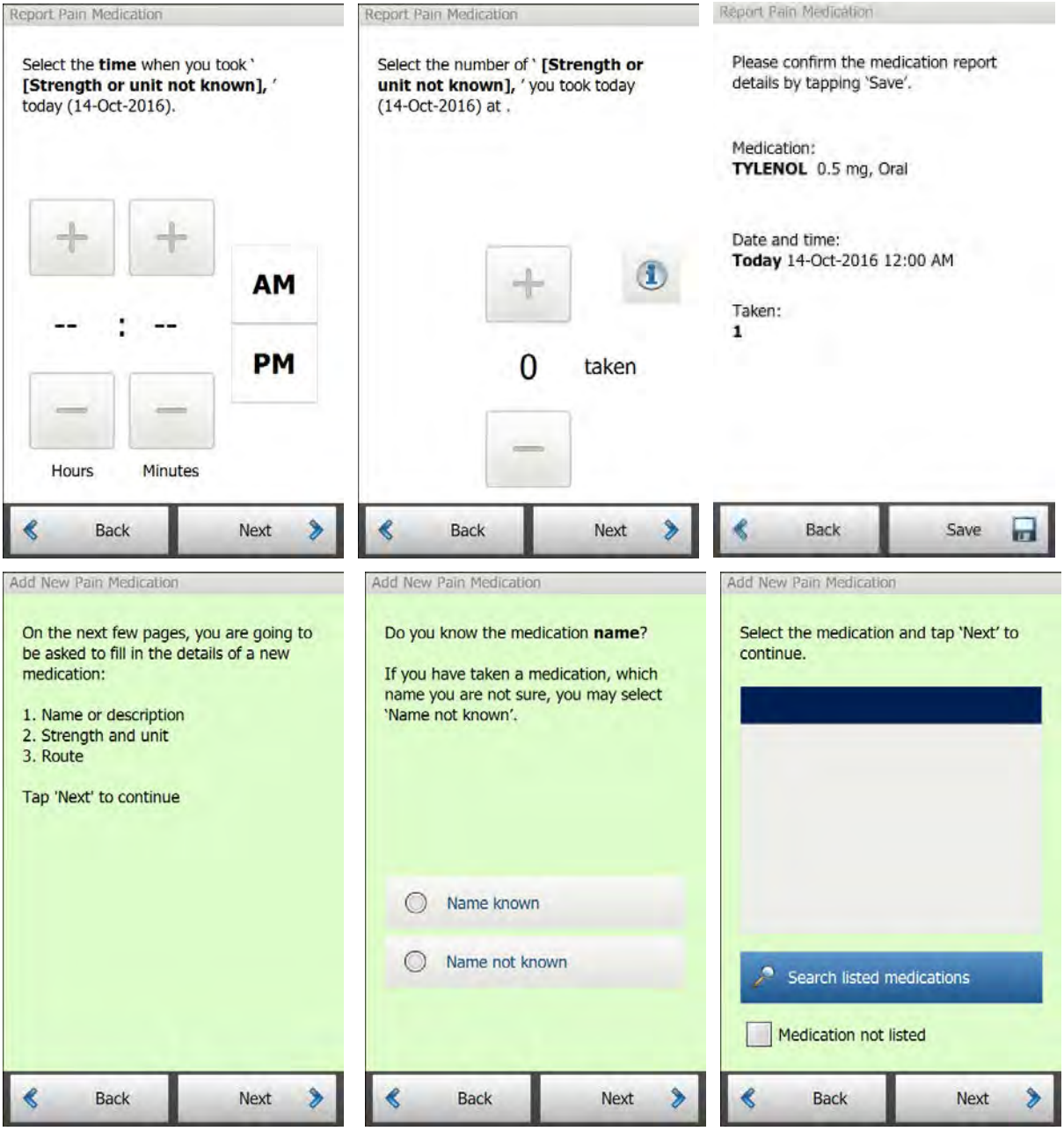

Menstrual Bleeding
01:57 PM
Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?
Yes
No
Back
Next

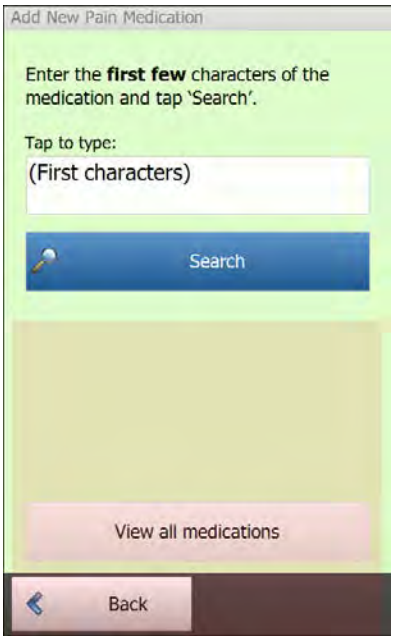

Use of Pain Medication
01:57 PM
Did you take any medication **today** to treat pain caused by your uterine fibroids?
Yes
No
Back
Next


Report Pain Medication
Tap below to report any Medication you have taken **today** to treat pain caused by your uterine fibroids
Report medication
Your recently **reported** medications:
Close


Report Pain Medication
On the next page select the taken medication from the list, and tap the green 'Next' button.
If you have taken a medication that is not listed, tap the **'I took a non-listed medication'** button.
Back
Next


Report Pain Medication
Select the taken **medication** from the list and tap the green **'Next'** button.
I took a non-listed medication
Back
Next

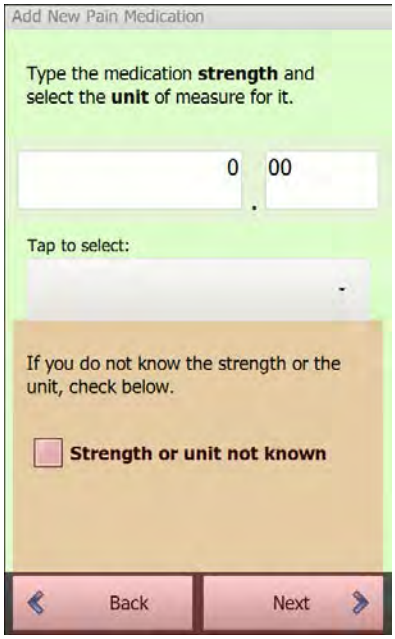

Report Pain Medication
Select the time when you took ' [Strength or unit not known], ' today (14-Oct-2016).
AM
PM
-- : --
Hours
Minutes
Back
Next
Report Pain Medication
Select the number of ' [Strength or unit not known], ' you took today (14-Oct-2016) at .
0 taken
Back
Next
Report Pain Medication
Please confirm the medication report details by tapping 'Save'.
Medication:
TYLENOL 0.5 mg, Oral
Date and time:
Today 14-Oct-2016 12:00 AM
Taken:
1
Back
Save
Add New Pain Medication
On the next few pages, you are going to be asked to fill in the details of a new medication:
1. Name or description
2. Strength and unit
3. Route
Tap 'Next' to continue
Back
Next
Add New Pain Medication
Do you know the medication name?
If you have taken a medication, which name you are not sure, you may select 'Name not known'.
Name known
Name not known
Back
Next
Add New Pain Medication
Select the medication and tap 'Next' to continue.
Search listed medications
Medication not listed
Back
Next

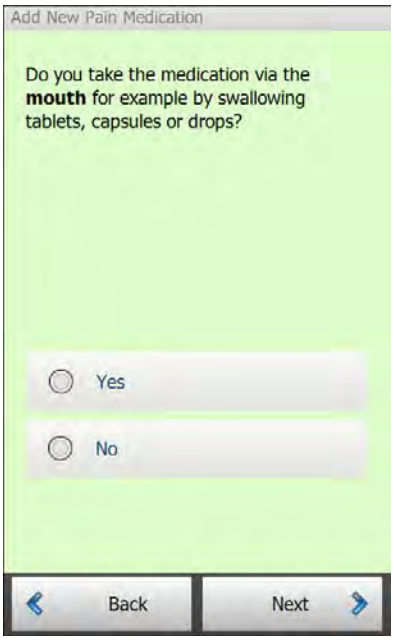

Add New Pain Medication
Enter the **first few** characters of the medication and tap 'Search'.
Tap to type:
(First characters)
Search
View all medications
Back


Add New Pain Medication
Select the medication and tap 'Next' to continue.
Medication not listed
Back
Next

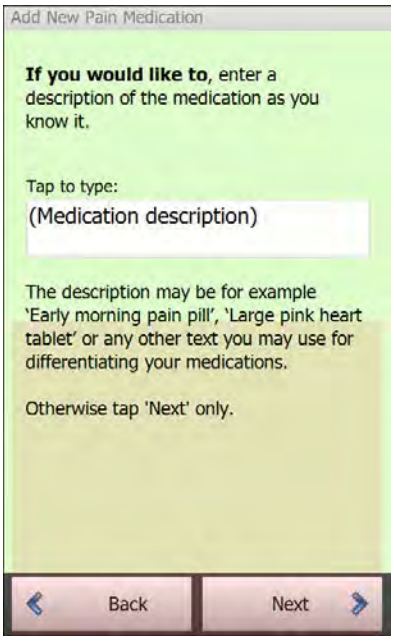

Add New Pain Medication
Please type the **name** of the medication **without** strength details.
Tap to type:
(Medication name)
Next
Back


Add New Pain Medication
Enter a description of the medication as you **know it**.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for identifying your medications.
Back
Next


Add New Pain Medication
Type the medication **strength** and select the **unit** of measure for it.
0
00
Tap to select:
If you do not know the strength or the unit, check below.
Strength or unit not known
Back
Next


Add New Pain Medication
Do you take the medication via the **mouth** for example by swallowing tablets, capsules or drops?
Yes
No
Back
Next


Add New Pain Medication
Select the **route** for the medication:
Back
Next


Add New Pain Medication
If you would like to, enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for differentiating your medications.
Otherwise tap 'Next' only.
Back
Next


Add New Pain Medication
Please confirm the medication details by tapping **'Save'.**
Back
Save


Medication saved
Your **new medication** has been added to your listed medications.
If you took the **added** medication **pain medicine [Strength or unit not known], Oral**, report the intake time and the amount taken by tapping **'Continue'**.
If you **did not** take the added medication, please tap **'Exit'** to go back to the reported medications.
Continue
Exit

Appendix 3. Menorrhagia Impact Questionnaire

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

Pt. Initials: _____ **Pt. ID:** _____

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐	☐	☐	☐	☐
10. Made you anxious about traveling?	☐	☐	☐	☐	☐
11. Interfered with your physical activities?	☐	☐	☐	☐	☐
12. Caused you to feel tired or worn out?	☐	☐	☐	☐	☐
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐	☐	☐	☐	☐
14. Made you feel as if you are not in control of your life?	☐	☐	☐	☐	☐
15. Made you concerned about soiling underclothes?	☐	☐	☐	☐	☐
16. Made you feel less productive?	☐	☐	☐	☐	☐
17. Caused you to feel drowsy or sleepy during the day?	☐	☐	☐	☐	☐
18. Made you feel self-conscious of weight gain?	☐	☐	☐	☐	☐
19. Made you feel that it was difficult to carry out your usual activities?	☐	☐	☐	☐	☐
20. Interfered with your social activities?	☐	☐	☐	☐	☐
21. Made you feel conscious about the size and appearance of your stomach?	☐	☐	☐	☐	☐
22. Made you concerned about soiling bed linen?	☐	☐	☐	☐	☐

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel wiped out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Diminished your sexual desire?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 5. European Quality of Life Five-Dimension Five-Level Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

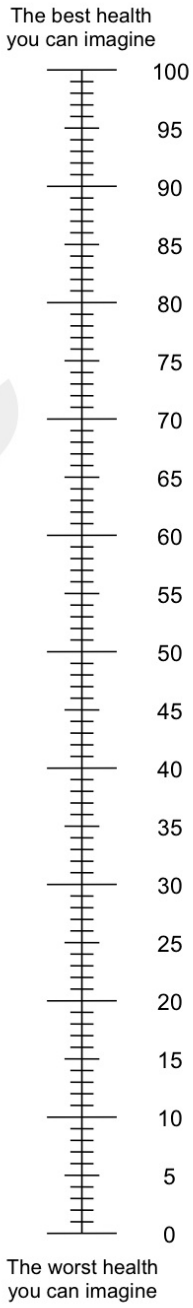
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6. Patient Global Assessments

Patient Global Assessment (for function)

How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. No limitation at all
2. Mild limitation
3. Moderate limitation
4. Quite a bit of limitation
5. Extreme limitation

Patient Global Assessment (for symptoms)

How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. Not severe
2. Mildly severe
3. Moderately severe
4. Very severe
5. Extremely severe

Appendix 7. Assessment of Abnormal Liver Function Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with low-dose estradiol and norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

h. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Appendix Table 1[a]; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • CBC with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.; • Serology for celiac disease; • Appropriate liver imaging; • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

STATISTICAL ANALYSIS PLAN

Study Titles:	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001 and MVT-601-3002
Indication:	Heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	IND # 131161 EudraCT # 2016-003727-27
Version/Effective Date:	Original: 07-May-2019 Amendment 1: 14-JUN-2019

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

MVT-601-3001 (LIBERTY 1): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

MVT-601-3002 (LIBERTY 2): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

This statistical analysis plan has been approved by Myovant Sciences GmbH ("Myovant"), with Myovant Sciences, Inc., acting as agent of Myovant. The following signatures document this approval.

[redacted]

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AMENDMENT 1: SUMMARY OF CHANGES

The purpose of the amendment is to update the gate-keeping mixed sequence testing procedure for the key secondary endpoints in the statistical analysis plan (SAP) for MVT-601-3002 (LIBERTY 2 study).

A single SAP was developed for the two pivotal phase 3 studies (LIBERTY 1 and 2) which was finalized on May 7, 2019 prior to database lock for the LIBERTY 1 study. The SAP pre-specified eight efficacy endpoints (primary and seven key secondary endpoints with alpha-protection) with the same hierarchal testing order for both studies. The LIBERTY 1 study has been unblinded and the Sponsor announced (on 14May2019) that the study met statistical significance for primary endpoint and 6 of the key secondary endpoints pre-specified in the testing procedure.

Based on the information from testing of the key secondary endpoints in LIBERTY 1, the SAP is being amended to increase the probability of technical success for LIBERTY 2 by modifying the gate-keeping mixed sequence testing procedure for LIBERTY 2 by switching the order for 2 of the key secondary endpoints: 1) the proportion of women with a hemoglobin ≤ 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24 and 2) the proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid-associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization. This change is being made while the LIBERTY 2 study blind is still in place using only information from the LIBERTY 1 results and while still testing the same list of alpha-protected 2nd endpoints. fdfd

A detailed list of changes is described below.

Item; Section(s)	Original	Amendment 1	Rationale
7.4.1	Hemoglobin increase > 2g/dL is 4th endpoint tested in fixed sequence following testing of endpoints 1,2 and 3; and max NRS score ≤ 1 is 5th endpoint tested as part of Hochberg procedure with endpoints 6 and 7.	Modified for LIBERTY 2: Max NRS score ≤ 1 is 4th endpoint tested in fixed sequence following testing of endpoints 1,2 and 3; and Hemoglobin increase > 2g/dL is 5th endpoint tested as part of Hochberg procedure with endpoints 6 and 7	The main purpose of the change in endpoint ordering is to increase the probability of success for LIBERTY 2 based on the information learned from the conduct of LIBERTY 1 with the following justifications: • The LIBERTY 2 study is on-going and the data remain blinded • There has been no interim assessment or analysis of the LIBERTY 2 data • The endpoints remain the same, but are reordered so the information about the endpoints is being systemically collected

Item; Section(s)	Original	Amendment 1	Rationale
			• No endpoint has been added or deleted • Since this amendment will be implemented prior to the data unblinding of the LIBERTY 2 study and there is no change to LIBERTY 2, the overall type I error rate for multiple comparisons for the LIBERTY 2 study is controlled.

16.1.9. Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

Study Titles:	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001 and MVT-601-3002
Indication:	Heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	IND # 131161 EudraCT # 2016-003727-27
Version/Effective Date:	Original: 07-May-2019 Amendment 1: 14-Jun-2019

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

MVT-601-3001 (LIBERTY 1): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

MVT-601-3002 (LIBERTY 2): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

This statistical analysis plan has been approved by Myovant Sciences GmbH ("Myovant"), with Myovant Sciences, Inc., acting as agent of Myovant. The following signatures document this approval.

PPD

14 Jun 2019
Date

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LIST OF ABBREVIATIONS

Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMD	bone mineral density
BMI	body mass index
C_τ	predose trough concentrations
CDF	cumulative distribution function
CFI	comparative fit index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DSMB	data safety monitoring board
DXA	dual-energy x-ray absorptiometry
E2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOT	end-of-treatment
EQ-5D-5L	European Quality of Life Five-Domain Five-Level
FP	feminine product
FPRR	feminine product return rate
FSH	follicle-stimulating hormone
GFI	goodness of fit index
Hgb	hemoglobin
ICH	International Council on Harmonisation
ITT	intent-to-treat
KM	Kaplan Meier
LH	luteinizing hormone
LLN	lower limit of normal
LS	least squares
max	maximum
MBL	menstrual blood loss
min	minimum
mITT	modified intent to treat

Term	Definition/Explanation
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
M-vol	myoma volume
NET	norethindrone
NETA	norethindrone acetate
NRS	Numerical Rating Scale
PBO	placebo
PDF	probability density function
PGA	patient global assessment
PK	pharmacokinetic
PT	Preferred Term
QD	once daily
QTcF	corrected QT interval Fridericia
RMSEA	root mean square error of approximation
SAP	statistical analysis plan
SD	standard deviation
SES	standardized effect size
SMQ	standard MedDRA query
SOC	System Organ Class
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
U-vol	uterine volume
WHO	World Health Organization
Wks	weeks

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the analyses planned for phase 3 studies MVT-601-3001 (LIBERTY 1) and MVT-601-3002 (LIBERTY 2), both entitled "An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids." In these studies, patients are randomized to one of three treatment arms: relugolix 40 mg + estradiol/norethindrone acetate (E2/NETA) 1 mg/0.5 mg for 24 weeks (Group A, also referred to as the relugolix + E2/NETA group), relugolix 40 mg for 12 weeks followed by 12 weeks of relugolix 40 mg + E2/NETA 1 mg/0.5 mg (Group B, also referred to as the relugolix + delayed E2/NETA group), or placebo for 24 weeks (Group C, also referred to as the placebo group).

The 2 phase 3 studies are replicative; the only difference between the two protocols is the Week 24 endometrial biopsies, which in MVT-601-3001 are done in all patients and in MVT-601-3002 depend on the results of the Week 24 ultrasound.

This SAP was developed in accordance with the International Council on Harmonisation (ICH) E9 guidelines. All decisions regarding statistical analysis of the study, as defined in this SAP, will be made prior to unblinding of the study data.

The SAP is based on:

- Protocol MVT-601-3001, Amendment 2, dated 18 Sept 2017;
- Protocol MVT-601-3002, Amendment 2, dated 25 Sept 2017;
- ICH guidelines E3 (Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

This document may evolve over time (eg, to reflect the requirements of protocol amendments or regulatory requests). However, the SAP is to be finalized, approved by the sponsor, and placed on file before the database is locked. Changes to the final approved plan will be noted in the clinical study report (CSR). Unless otherwise specified, the objectives, definitions of endpoints, and pre-specification of analyses presented in this document apply to both studies.

1.1. Study Objectives and Endpoints

The study objectives and corresponding endpoints are listed in the following table. The endpoints in *italics* are not listed in the protocol, but they have been identified as important for assessment of treatment effect on the basis of emerging data and clinical relevance to the study objectives and therefore are included in this SAP.

Table 1: Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary Efficacy	
To determine the benefit of relugolix 40 mg once daily co-administered with E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids	Proportion of women in the relugolix + E2/NETA group versus the placebo group who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method
Key Secondary Efficacy (Alpha-Protected for Hierarchical Hypothesis Testing — relugolix + E2/NETA versus placebo)	
Achievement of amenorrhea	Proportion of women who achieve amenorrhea over the last 35 days of treatment
Heavy menstrual bleeding associated with uterine fibroids	Percent change from Baseline to Week 24 in MBL volume
Impact of uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the UFS-QoL	*Change from Baseline to Week 24 in the UFS-QoL Bleeding and Pelvic Discomfort Scale score, a sub-scale of the UFS-QoL Symptom Severity scale*
Change in hemoglobin	*Proportion of women with a hemoglobin ≤ 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline to Week 24*
Pain associated with uterine fibroids	*Proportion of patients with a maximum NRS score ≤ 1 during the last 35 days before the last dose of study drug in the subset of women with a maximum NRS score ≥ 4 for pain associated with uterine fibroids during the last 35 days prior to randomization*
Uterine fibroid volume	Percent change from Baseline to Week 24 in uterine fibroid volume
Uterine volume	Percent change from Baseline to Week 24 in uterine volume
Other Secondary Efficacy (Not for Hierarchical Hypothesis Testing) [a]	
To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids	Proportion of women in the relugolix + delayed E2/NETA group versus the placebo group who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method
Heavy menstrual bleeding associated with uterine fibroids	• *Percent change from Baseline in MBL volume by visit* • *Change from Baseline in MBL volume by visit*

Objective(s)	Endpoint(s)
	• Time to achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume as measured by the alkaline hematin method • *Proportion of women in the relugolix + E2/NETA group versus the placebo group who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume by visit*
Achievement of amenorrhea	• *Sustained amenorrhea rate by visit* • *Time to achieving sustained amenorrhea* • *Time to achieving amenorrhea*
Change in hemoglobin	• Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24 • *Change from Baseline to Week 24 in hemoglobin for women with a hemoglobin ≤ 10.5g/dL at Baseline*
Impact of uterine fibroids on symptoms, activities and health-related quality of life as measured by components of the UFS-QoL	• Change from Baseline to Week 24 in the UFS-QoL Symptom Severity Scale score • Change from Baseline to Week 24 in the UFS-QoL Activities Scale score • *Change from Baseline to Week 24 in the UFS-QoL Revised Activities Scale score* • *Proportion of responders who achieved a meaningful increase of at least 20 points from Baseline to Week 24 in UFS-QoL Revised Activities Scale score* • *Proportion of responders who achieved a meaningful reduction of at least 20 points from Baseline to Week 24 in UFS-QoL Bleeding and Pelvic Discomfort Scale score* • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QoL Question 11 • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QoL Question 20

Objective(s)	Endpoint(s)
	• Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QoL Question 29
Patient global assessment for function and symptoms as measured by the PGA for function and symptoms	• Change in PGA for uterine fibroid related function from Baseline to Week 24 • Change in PGA for uterine fibroid symptoms from Baseline to Week 24 • *Proportion of patients achieving improvement from Baseline in PGA for uterine fibroid symptoms from Baseline to Week 24* • *Proportion of patients achieving improvement from Baseline in PGA for uterine fibroid related function from Baseline to Week 24*
Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire	• Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities
Pain associated with uterine fibroids[b]	Proportion of women who achieve a *maximum* NRS score for pain associated with uterine fibroids over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization
Safety	
To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks	Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms
To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in the relugolix + E2/NETA group compared with the relugolix + delayed E2/NETA group in women with heavy menstrual bleeding associated with uterine fibroids	Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in the relugolix + E2/NETA group compared with relugolix + delayed E2/NETA group as assessed by DXA

Objective(s)	Endpoint(s)
To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks	Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA
To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg in women with heavy menstrual bleeding associated with uterine fibroids	Incidence of vasomotor symptoms
Pharmacokinetic and Pharmacodynamic	
To evaluate the pharmacokinetic and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg	• Predose trough concentrations (C_τ) of relugolix, and NET and Baseline-adjusted E2 concentration • Absolute and changes from Baseline to Week 24 in predose concentrations of LH, FSH, E2, and progesterone
Exploratory	
To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg compared with placebo on patient-reported quality of life outcome measures (EQ-5D-5L)	Change from Baseline to Week 24 in the EQ-5D-5L Scale score

Abbreviations: DXA, dual energy x-ray absorptiometry; E2, estradiol; EQ-5D-5L, European Quality of Life Five-Domain Five-Level; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MBL, menstrual blood loss; NET, norethindrone; NETA, norethindrone acetate; NRS, numerical rating scale; PGA, Patient Global Assessment; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life.

[a] The secondary endpoints below will be assessed comparing the relugolix + E2/NETA group with the placebo group inferentially; the relugolix + E2/NETA group to the relugolix + delayed E2/NETA group and the relugolix + delayed E2/NETA group to the placebo group descriptively, unless otherwise specified.

[b] Changed from mean NRS score (in the protocol) to maximum NRS score. Since pain associated with uterine fibroids is mostly during menstrual days, mean NRS scores over the last 35 days is very low (< 1) for most patients, hence, not appropriate to define percent reduction from Baseline.

2. STUDY DESIGN

2.1. Summary of Study Design

The LIBERTY 1 and LIBERTY 2 studies are two replicate, randomized, double-blind, placebo-controlled phase 3 studies evaluating the efficacy and safety of relugolix 40 mg in combination with E2 1 mg/NETA 0.5 mg in women with heavy menstrual bleeding associated with uterine fibroids (MVT-601-3001, MVT-601-3002). Patients with heavy menstrual bleeding associated with uterine fibroids — as evidenced by a menstrual blood loss (MBL) volume of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during one cycle, as measured by the alkaline hematin method during the screening period — who met other eligibility criteria were randomly assigned (1:1:1) to 1 of the 3 treatment arms:

- Group A (relugolix + E2/NETA): relugolix 40 mg once daily co-administered with E2 1 mg/NETA 0.5 mg for 24 weeks;
- Group B (relugolix + delayed E2/NETA): relugolix 40 mg once daily for 12 weeks followed by relugolix 40 mg once daily co-administered with E2 1 mg/NETA 0.5 mg for 12 weeks;
- Group C (placebo): placebo for 24 weeks

Randomization was stratified as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening MBL volume using alkaline hematin method: < 225 mL versus ≥ 225 mL.

The primary endpoint for both trials is the proportion of women receiving relugolix + E2/NETA (Group A) versus placebo (Group C) who achieve BOTH a MBL volume of < 80 mL AND at least a 50% reduction from Baseline in MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method.

This study includes a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a safety follow-up period (~30 days). During the screening period, diagnoses of uterine fibroids are confirmed by centrally reviewed transvaginal ultrasound. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during the screening period are treated with oral or parenteral iron replacement therapy. After randomization, patients begin double-blinded study drug treatment for 24 weeks.

Patients who complete LIBERTY 1 or LIBERTY 2, including those randomized to placebo, and who meet other eligibility criteria are offered the opportunity to enroll in a 28-week open-label extension study, in which all patients will receive relugolix 40 mg co-administered with E2 1 mg and NETA 0.5 mg. Patients who do not enroll into the extension study have a safety follow-up visit approximately 30 days after their last doses of study medication.

Additional safety follow-up may be performed after the safety follow-up visit. Data collected during the additional safety follow-up period will be summarized and reported in an addendum to the respective clinical study report. Patients who are not proceeding into the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy should be treated as per standard of care and additional follow-up should be evaluated and managed, as

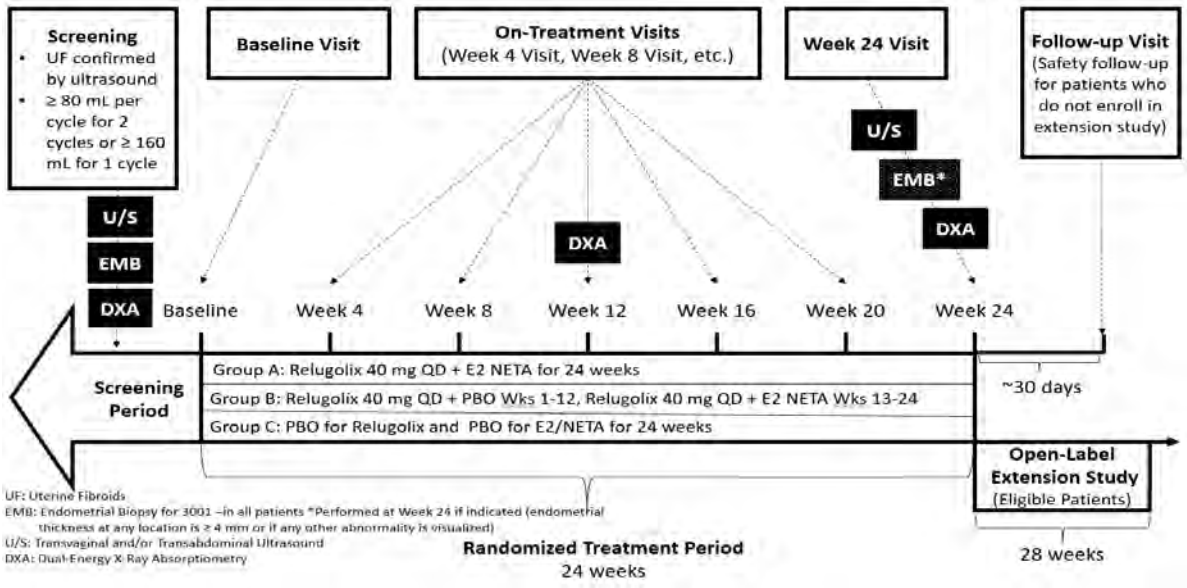
needed, by a gynecologist. In addition, they should undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory.

Patients who are not proceeding into the extension study and who have a bone mineral density (BMD) loss of > 2% at the lumbar spine (L1–L4) or total hip relative to the Baseline measurement at their Week 24/Early Termination visit will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc.) that might affect BMD through the time of the repeat DXA scan. If the DXA scan 6 months post-treatment continues to show BMD loss of > 1.5% at the lumbar spine and/or > 2.5% at the total hip compared with Baseline, patients will have an additional scan at 12 months post-treatment. All follow-up DXA scans will be submitted for central reading. Patients whose menses had not resumed as of the safety follow-up visit for unexplained reasons will be contacted by telephone to determine if menses have resumed. Patients with reductions in visual acuity will be referred for ophthalmology consultation.

An external independent data and safety monitoring board (DSMB) was established to review periodic safety analyses, including BMD assessments. The roles and responsibilities of the independent DSMB are described in a separate charter. A separate SAP was created to document the specific safety data analyses that would be performed by an independent data coordinating center for the DSMB on an ongoing basis during the study.

A schematic of the study is presented in Figure 1.

Figure 1: Study Schematic



Abbreviations: E2, estradiol; NETA, norethindrone; PBO, placebo; QD, once daily; Wks, weeks.

2.2. Sample Size Considerations

2.2.1. Sample Size Justifications for Primary Efficacy Endpoint

The following assumptions were used to determine the sample size for this study:

- 2-sided type I error rate: 0.05
- Randomization: 1:1:1
- Responder rate for placebo group: 25%
- Difference in responder rates between the relugolix + E2/NETA group and the placebo group: 30%
- Dropout rate: ~20%

With the assumption of a dropout rate of 20%, approximately 130 women in the relugolix + E2/NETA group and 130 women in the placebo group will provide at least 99% power at a 2-sided 0.05 significance level to detect a 30% difference in responder rates between relugolix + E2/NETA group and the placebo group for the primary endpoint. With an additional 130 women in the relugolix + delayed E2/NETA group, the total sample size will be approximately 390 women.

The assumed responder rate of 25% for the placebo group is within the range of responder rates observed from similar phase 3 trials in uterine fibroids (Stewart, 2017). The sample size and power calculations are based on a chi-squared test.

2.2.2. Sample Size Justifications for Percent Change in Bone Mineral Density at 12 Weeks

A pooled analysis of the percent change in BMD at 12 weeks using data from both phase 3 studies is described separately in the statistical analysis plan for the Integrated Summary of Safety. The results of this pooled analysis comparing the relugolix + E2/NETA group with the relugolix + delayed E2/NETA group will be presented in the Integrated Summary of Safety and will not be included in the CSRs for these studies.

For the comparison of the relugolix + E2/NETA group with the relugolix + delayed E2/NETA group with respect to the percent change in BMD from Baseline to Week 12 at the lumbar spine (L1–L4), approximately 260 women in the relugolix + E2/NETA group (pooled between the LIBERTY 1 and LIBERTY 2 studies) and 260 women in the relugolix + delayed E2/NETA (pooled) will provide at least 90% power at a 2-sided 0.05 significance level to detect a 1.25% absolute treatment difference, assuming a standard deviation of 4% and up to 15% dropout rate for each treatment group. Power calculations for this BMD comparison are based on a two-sample t-test.

Sample size and power calculations were performed using the software package *nQuery* 4.0 (Statistical Solutions Ltd.).

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim efficacy analyses were planned or performed for these two studies.

An external, independent DSMB was established to review periodic safety analyses, including BMD assessments. A separate SAP was created to document the specific safety data analyses that would be performed by an independent data coordinating center for the DSMB on an ongoing basis during the study.

3.2. Final Analyses

The final analysis of all efficacy and safety data from MVT-601-3001 and MVT-601-3002 will occur after approximately 390 patients have been randomized to each study and have had the opportunity to be followed for 24 weeks of study treatment and through the 30-day safety follow-up visit. This document describes this final analysis.

There will be periodic safety data review by the DSMB. An independent data coordinating center has performed the periodic safety analyses and has provided results of these analyses to the DSMB, as defined in the DSMB charter and outlined in a separate DSMB SAP.

3.3. Safety Follow-Up Analyses

Patients who are not proceeding into the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy should be treated as per standard of care and additional follow up should be evaluated and managed, as needed, by a gynecologist. In addition, they should undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory.

Patients who are not proceeding into the extension study and who have a BMD loss of > 2% at the lumbar spine (L1–L4) or total hip relative to the Baseline measurement at their Week 24/Early Termination visit will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scan. If the DXA scan 6 months post-treatment continues to show BMD loss of > 1.5% at the lumbar spine and/or > 2.5% at the total hip compared to Baseline patients will have an additional scan at 12 months post-treatment. All follow-up DXA scans will be submitted for central reading. Patients whose menses had not resumed as of the safety follow-up visit for unexplained reasons will be contacted by telephone to determine if menses have resumed. Patients with reductions in visual acuity will be referred for ophthalmology consultation.

Data collected during the additional safety follow-up period will be summarized and reported in an addendum to the respective clinical study report.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING OF MISSING DATA

4.1. Data Presentation Conventions

All statistical analyses will be conducted using SAS® Version 9.2 or higher.

A statistical test for the primary and secondary efficacy endpoints will be assessed at a two-sided $\alpha = 0.05$ significance level, and all confidence intervals (CIs) will be reported as two-sided unless otherwise stated.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. For continuous variables, the number of patients with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values will be tabulated.

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value; if the measured value is large (eg, > 100), fewer decimal places may be displayed.
- Percentages will be rounded to 1 decimal place;
- p-values will be rounded to 4 decimal places. p-values < 0.0001 will be presented as "< 0.0001" and p-values > 0.9999 will be presented as "> 0.9999";
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded to 1 decimal place;
- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded to 1 decimal place;
- Age will be calculated using the date of randomization. If only year of birth is collected, 1 July of the year of birth will be used to calculate age.
- 1 pound = 0.454 kg;
- 1 inch = 2.54 cm;
- Missing efficacy or safety data will not be imputed unless otherwise specified;
- For laboratory results above or below sensitivity limits displayed as "<" or ">" a quantification threshold, 0.0000000001 will be subtracted or added, respectively, to the threshold to derive a numeric result for analyses;
- For MBL volume reported as below the limit of quantification (for example, MBL below Quantification Level <5.0 mL or <2.5 mL), 0.0000000001 will be subtracted from the reported quantification threshold for the visit to derive a numeric result for analyses;
- For safety analyses, calculation of percentages will be calculated on the basis of the number of patients in the analysis population in each treatment group;

- For by-visit observed data analyses, calculation of percentages will be calculated on the basis of the number of patients with non-missing data as the denominator, unless otherwise specified;
- For other continuous endpoints, the summary statistics will include mean, SD, median, and range (minimum and maximum);
- For time-to-event endpoints, the summary statistics will include median time to event-free survival, 25th and 75th percentiles and number of patients at risk at specified time points;
- For categorical endpoints, the summary statistics will include counts and percentages;
- Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, exact methods will be employed, unless otherwise specified.

4.2. Analysis Populations

Three analysis populations are defined below. Number and percent of patients meeting the definition of each analysis population will be summarized by treatment group.

4.2.1. Modified Intent-to-Treat Population

Efficacy analyses will be performed using the modified Intent-to-Treat (mITT) population, unless otherwise specified. The mITT population is defined as all randomized patients who have received any amount of study drug (relugolix/placebo or E2/NETA/placebo). Efficacy analyses will be performed by treatment group as randomized.

4.2.2. Per-Protocol Population

The Per-Protocol population will consist of those members of the mITT population who do not have any of the specified subset of important protocol deviations (see Section 5.3).

The Per-Protocol population will not be analyzed if this population comprises > 95% or < 50% of the mITT population. The Per-Protocol population will be used for sensitivity analysis of the primary efficacy endpoint. The Per-Protocol population and the associated subset of important protocol deviations will be identified prior to unblinding the trial.

4.2.3. Safety Population

Safety analyses will be performed using the Safety population unless otherwise specified. The Safety population is the same as the mITT population and is defined as all randomized patients who have received any amount of study drug. Safety data will be analyzed by treatment group according to the actual treatment received (not the randomized treatment). Any patient who received at least one dose of relugolix will be considered as a relugolix patient.

4.3. Definitions, Computation, and Convention

4.3.1. Definition of Date of First Dose and Date of Last Dose of Study Drug

The date of the first dose of study drug is defined as the date when a patient receives the first dose of study drug (relugolix/placebo or E2/NETA/placebo). The date of the last dose of study

drug is defined as the date a patient receives the last dose of study drug. If the complete date of last dose of study drug is unknown, the last date the study drug was known to have been taken will be used.

4.3.2. Study Day

Study day will be calculated with respect to the date of the first dose of study drug (Study Day 1). For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as:

(Assessment date – date of first dose of study drug) + 1

For assessments conducted before the date (and time) of the first dose of study drug, study day will be calculated as:

(Assessment date – date of first dose of study drug)

For patients who do not receive any amount of study drug, study day will be calculated as above with respect to the date of randomization.

4.3.3. Definition of Treatment Duration

Treatment duration is defined as the duration of time from the date of the first dose of study drug to the date of the last dose of study drug as follows:

(Date of last dose of study drug – Date of first dose of study drug) + 1

For patients without complete date of last dose of study drug, the last date study drug was known to have been taken will be used to calculate treatment duration. For patients who did not return for the Early Termination visits, the time after their last visit will not be included in calculations of treatment duration.

4.3.4. Definition of Baseline Value and Post-Baseline Value

Unless otherwise specified, Baseline values are defined as the last measurement before the first administration (date and time) of study drug. A post-Baseline value is defined as a measurement taken after the first administration of study drug. Change from Baseline is defined as (post-Baseline value – Baseline value). Both date and time of study drug administration and measurement will be considered when calculating Baseline value. If the time is not available, then the date alone will be used. For patients who receive no study medication, the date of randomization will be used in place of the date of first dose in determining Baseline and post-Baseline values.

4.3.5. Visit Windows

Visit windows, which will be used to associate assessments with a scheduled visit, will be used only for summarizing data by visit. The windows for scheduled assessments are shown in Table 2, Table 3 (electrocardiogram [ECG], BMD, Uterine Fibroid Symptom and Health-Related Quality of Life [UFS-QoL]), and Table 4 (transvaginal ultrasound, endometrial biopsy, and European Quality of Life Five-Domain Five-Level [EQ-5D-5L]), respectively. For both efficacy and safety assessments, the study day will be used to determine the associated visit window.

The data collected in the electronic diary (eDiary) related to bleeding and use of feminine products will be assigned to visit windows as specified in Table 5 and will be used to calculate the feminine product return rate (FPRR) as specified in Section 7.3.3.

If the results from more than one monthly or Week 12/Week 24 assessment are within a given visit window, the non-missing result from the assessment closest to the target date will be used. If two assessments are equally close to the target day, the earlier assessment will be used. For summaries of shift from Baseline in safety parameters, all values will be considered for these analyses.

Table 2: Visit Windows for Monthly Assessments

Visit	Start Day	Target Day	End Day
Week 4[a]	1	29	43
Week 8	44	57	71
Week 12	72	85	99
Week 16	100	113	127
Week 20	128	141	155
Week 24	156	169	196
Safety Follow-Up[b]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

[a] Start day of Week 4 for study day 1 includes only post-Baseline assessments that occurred after the first dose.

[b] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids.

Table 3: Visit Windows for Week 12/Week 24 Assessments (ECG, BMD, UFS-QoL)

Visit	Start Day	Target Day	End Day
Week 12	64	85	106
Week 24	148	169	196
Safety Follow-up[a]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

Abbreviations: BMD, bone mineral density; ECG, electrocardiogram; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life.

[a] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids

Table 4: Visit Windows for Week 24 Assessments (Transvaginal Ultrasound, Endometrial Biopsy, EQ-5D-5L)

Visit	Start Day	Target Day	End Day
Week 24	128	169	196
Safety Follow-up[a]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

Abbreviations: EQ-5D-5L, European Quality of Life Five-Domain Five-Level.

[a] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids.

Table 5: Time Window for eDiary and Feminine Product Collection

Visit	Feminine Product Collection Visit Date[a,b]	Time Window[a]
Week 4	X_1	(Date of Study Day 1) - < X_1
Week 8	X_2	(X_1 +1) - ≤ X_2
Week 12	X_3	(X_2 +1) - ≤ X_3
Week 16	X_4	(X_3 +1) - ≤ X_4
Week 20	X_5	(X_4 +1) - ≤ X_5
Week 24	X_6	(X_5 +1) - ≤ X_6
Week 24/EOT	X_{Last}[c]	(Previous Feminine Product Returned Visit +1)] – ≤ X_{Last}

[a] If feminine products are collected at more than 1 visit within a given visit window (Table 2), the last feminine product collection date will be used to define the time window. If the patient missed the previous visit, a planned study visit date will be used to calculate the window.

[b] In the absence of feminine product collection due to amenorrhea the visit date when amenorrhea was reported will be used.

[c] Date of last non-missing feminine product collection within the interval from (last dose date – 35) to (last dose date + 7 days) (see Section 7.3.3).

4.4. General Rules for Missing Data

Handling of missing data for the primary efficacy analysis is described in Section 7.3.5.

4.4.1. By-Visit Endpoints

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

4.4.2. Adverse Events and Concomitant Medications

The following imputation rules for the safety analyses will be used to address the issues with partial dates. The imputed dates will be used to determine the treatment-emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end dates of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default.

The following rules will be applied to impute partial dates for adverse events:

- If start date of an adverse event is partially missing, impute as follows:
  - If both Month and Day are missing and Year = Year of treatment start date, then set to treatment start date as long as adverse event end date is not prior to treatment start date;
  - If both Month and Day are missing and Year ≠ Year of treatment start date, then set to January 1;
  - If Day is missing and Month and Year = Month and Year of treatment start date, then set to treatment start date as long as adverse event end date is not prior to treatment start date;
  - If Day is missing and Month and Year ≠ Month and Year of treatment start date, then set to first of the month;
  - If start date is completely missing, set to treatment start date as long as adverse event end date is not prior to treatment start date.
- If end date of an adverse event is partially missing, impute as follows:
  - If both Month and Day are missing, then set to December 31;
  - If only Day is missing, then set to last day of the month;
  - If end date is completely missing, do not impute.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both).

The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both Month and Day are missing, then set to January 1;

  - If only Day is missing, then set to the first of the month.
- If end date of a medication is partially missing, impute as follows:
  - If both Month and Day are missing, then set to December 31;
  - If only Day is missing, then set to last day of the month.

If start date or end date of a medication is completely missing, do not impute.

5. STUDY POPULATION

5.1. Subjects Disposition

The number of patients for each of the following categories will be summarized by treatment group:

- All randomized patients;
- Patients included in the Safety population;
- Patients who completed the 12-Week randomized treatment period;
- Patients who completed the 24-Week randomized treatment period;
- Patients who discontinued early from the 24-Week randomized treatment period and reasons for discontinuation;
- Patients who enrolled in the extension study;
- Patients who entered the Post-Treatment Follow-Up Period and did not enroll in the extension study.

Patient disposition will be summarized for all randomized patients. Summaries will include the number and percentage of patients in the mITT and Safety populations. The number and percentage of patients who prematurely discontinue study drug and the reasons for discontinuation will be summarized by treatment group. The number and percentage of patients who continue into the extension study (MVT-601-3003) will also be summarized by treatment group.

5.2. Screen Failure

Reasons for screen failure will be summarized. Number and percentage of patients who did not pass screening will be based on the patients who signed the informed consent form but were not randomized.

5.3. Protocol Deviations

Protocol deviations will be categorized as important or minor per the protocol deviation plan. Important protocol deviations will include, but will not be limited to, the following categories:

- Randomized patient who did not satisfy key entry criteria;
- Randomized patient who met withdrawal criteria during the study but was not withdrawn;
- Randomized patient who received the wrong treatment;
- Randomized patient who received a prohibited concomitant medication that met criteria for an important protocol deviation;
- Unintentional unblinding of treatment assignment.

Important protocol deviations will be summarized by deviation category for all patients in the mITT population. A patient listing of all important protocol deviations will be provided.

In addition, patient eligibility, including inclusion criteria that are not met and exclusion criteria that are met at randomization enrollment, will be summarized for all patients in the mITT population.

A selected subset of the major protocol deviations that are likely to affect analysis of efficacy will be identified to define the Per-Protocol population prior to the database lock. This subset will include but will not be limited to the following important protocol deviations:

- Did not satisfy key entry criteria **(**restricted to patients with missing Baseline MBL volume or ineligible Baseline MBL volume);
- Drug compliance < 75%;
- Patient received prohibited concomitant medications that met criteria for important protocol deviation: restricted to patients who received prohibited concomitant medications that may cause significant drug-drug interaction;
- Unintentional unblinding of treatment assignment.

5.4. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by treatment group for the mITT population. Categorical data will be summarized using frequencies and percentages, by treatment group and overall (see Table 6 below). Summaries of continuous data will display the mean, SD, median, minimum, and maximum. The numbers of missing values will also be summarized.

Table 6: Categories for Demographic and Baseline Characteristics

Variable	Category
Age (years)	< 40, ≥ 40
Geographic region	North America, Rest of World
Race	Black or African American, White, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino or Not reported
BMI (kg/m^2) at Baseline	< 18.5, 18.5 to <25, 25 to <30, 30 to < 35, 35 to < 40, ≥ 40
History of prior pregnancy	Yes, No
Disease duration of uterine fibroid (years)	Min to <1, ≥ 1 to < 3, ≥3 to <5, ≥5 to <10, ≥ 10
Type of uterine fibroids	
Subserous fibroid	Yes, No
Intramural fibroid	Yes, No
Submucosal fibroid	Yes, No
Other	Yes, No
Any surgery for uterine fibroids	Yes, No
Volume of myoma at Baseline (cm^3)	< 25, ≥ 25
Volume of uterus at Baseline (cm^3)	< 300, ≥ 300
Menstrual blood loss volume at Baseline (mL)	< 225, ≥ 225
Menstrual blood loss volume at Baseline (mL)	< 160, ≥ 160
Hemoglobin at Baseline (g/dL)	Min to < 8, ≥ 8 to <10.5, ≥ 10.5 to <12, ≥ 12
UFS-QoL Bleeding and Pelvic Discomfort Scale	0 to < 25, 25 to <50, 50 to <75, 75 to 100
Maximum NRS score for uterine fibroid-associated pain at Baseline	< 4, ≥ 4
Patient Global Assessment	
Function	No limitation at all, mild limitation, moderate limitation, quite a bit of limitation, extreme limitation
Symptoms	Not severe, mildly severe, moderately severe, very severe, extremely severe

Abbreviations: BMI = body mass index; NRS = Numerical Rating Scale; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.

5.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term (PT). Additionally, summaries of uterine fibroid–specific medical and surgical treatment history will be provided. A patient with multiple occurrences of medical history within a PT will be counted only once in that PT.

5.6. Prior Medications and Concomitant Medications

Prior medications and concomitant medications taken during the study treatment period will be summarized for all patients in the Safety population by treatment group. Medications are considered concomitant if exposure occurs during the treatment period.

The number and percentage of patients who took at least one dose of a prior medication for treatment of uterine fibroids will be summarized by treatment group and overall using the World Health Organization (WHO) Drug Dictionary and summarized according to the Anatomical Therapeutic Chemical (ATC) Classification System and generic medication name. A patient who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6. STUDY DRUG EXPOSURE AND COMPLIANCE

Patients in the Safety population will be summarized for extent of exposure and compliance to study drug by actual treatment received. Exposure to and compliance with relugolix (or relugolix placebo) and E2/NETA (or placebo) will be summarized separately and will be based on the drug accountability case report forms.

Study drug exposure summaries will include the total dosage taken in milligrams, the total number of tablets (or capsules) taken, and the treatment duration.

Study drug compliance will be summarized for the treatment period and will be calculated as follows:

(total tablets taken / total tablets expected to be taken) x 100

The total tablets taken will be calculated as:

(total tablets dispensed - total tablets returned)

The total tablets expected to be taken is calculated as the total number of tablets a patient is expected to take each day times the length of time (in days) that the patient was in the treatment period of the study. Tablets that were dispensed and not returned will be assumed to have been taken. For patients who did not return for their last scheduled visit, tablets that were dispensed and not returned will not be included in the calculation of study drug compliance. For patients who did not return for any post-Baseline visits and did not return dispensed study drug, study drug compliance will not be calculated and will be categorized as “not able to calculate” in summaries of study drug compliance.

Summary statistics of study drug compliance (eg, mean, median, etc.) will be presented, along with a categorical summary (eg, ≤ 80%, 80 to 100%, > 100%).

7. EFFICACY ANALYSES

7.1. General Considerations

Efficacy analyses will be conducted on the mITT population according to the randomized treatment assignment. Stratified analyses will incorporate the randomization stratification factors. If the group of patients at any factor level from a randomization stratification factor (eg, patients with Baseline MBL volume ≥ 225 mL) comprises < 10% of the entire mITT population, this stratification factor (eg, Baseline MBL volume) will not be used for stratified analyses. In addition, if there are < 15 patients in 1 of the 4 strata (derived from the 2 stratification factors each with 2 levels), only stratification factor of Baseline MBL volume (< 225 versus ≥225 mL) will be used in the stratified analysis for more robust strata-adjusted estimation of treatment effect. The stratification category used at the time of randomization (in the Interactive Web Recognition Service [IWRS] system) will be used for all analyses rather than data recorded on the electronic case report form (eCRF) unless otherwise specified. A sensitivity analysis of the primary endpoint will be performed if the data in the IWRS and eCRF for stratification factors differ by > 5%.

7.1.1. Analyses for Binary Data and Other Categorical Data

Binary data will be summarized by frequency counts and percentages for each treatment group.

7.1.2. Analyses for Categorical Data

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

7.1.3. Analyses for Continuous Data

Continuous variables will be summarized using descriptive statistics (eg, *n*, mean, median, SD, minimum, maximum, and first and third quartiles). For the analyses of change from Baseline, the mean at Baseline will be calculated for all patients with at least one post-Baseline value by treatment group. Additionally, the mean will also be calculated for each visit, including only the patients who are in the analysis who have data for that visit by treatment group.

7.1.4. Analyses for Time to Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method. The median, quartiles, and probabilities of an event at particular time points will be estimated by the Kaplan-Meier method.

Confidence interval for the Kaplan-Meier estimation is calculated using the exponential Greenwood formula via log-log transformation of the survival function.

The variance of the treatment difference will be calculated using the following formula:

$$V\left[\widehat{S_R}(t) - \widehat{S_L}(t)\right] = \hat{V}\left[\widehat{S_R}(t)\right] + \hat{V}[\widehat{S_L}(t)];$$

where each of the component of the variance of the Kaplan-Meier estimate will be calculated using Greenwood's formula:

$$\hat{V}[\hat{S}(t)] = \hat{S}(t)^2 \sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}$$

where n_i denotes the number of patients at risk at time t_i, and d_i denotes the number of events observed at time t_i.

The 95% CI of the treatment difference will be calculated using a log-log transformation of the difference in survival function, as follows:

$$[(\widehat{S_R}(t) - \widehat{S_L}(t))^{exp(1.96\,\hat{\tau}(t))}, (\widehat{S_R}(t) - \widehat{S_L}(t))^{exp(-1.96\,\hat{\tau}(t))}]$$

$$\text{where } \hat{\tau}^2(t) = \frac{\hat{V}[\widehat{S_R}(t) - \widehat{S_L}(t)]}{\{[\widehat{S_R}(t) - \widehat{S_L}(t)]\log[\widehat{S_R}(t) - \widehat{S_L}(t)]\}^2}.$$

A stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

7.2. Multiplicity Adjustment

The primary and the ranked secondary efficacy analyses will be performed at an overall alpha level of 0.05 (two-sided) comparing relugolix + E2/NETA (Group A) with placebo (Group C). A test will be deemed statistically significant if the two-sided p-value rounded to four decimal places is < 0.05. A gate-keeping testing procedure will be applied to maintain the family-wise type I error rate for the testing of primary and ranked secondary endpoints (see Section 7.4.1 for details).

Comparative statistics (p-values, 95% CIs for differences) will be provided for the treatment comparison of relugolix + E2/NETA with placebo for all other secondary efficacy endpoints. A treatment comparison of relugolix + delayed E2/NETA (Group B) with placebo will be performed only for the primary efficacy endpoint. There will be no statistical testing for treatment differences between the relugolix groups (Group A versus Group B) for any efficacy endpoints. The relugolix + E2/NETA group and relugolix + delayed E2/NETA group will be compared for the following safety endpoints: percent change from Baseline to Week 12 in BMD and incidence of vasomotor symptoms by 12 weeks (see Section 9.3.5 and Section 9.1.7, respectively). The above comparative analyses are not part of the gate-keeping testing procedure for label claims. p-values for primary and key secondary endpoints were adjusted for multiplicity. All other p-values are provided at a nominal level of 0.05.

7.3. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the proportion of women who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline in MBL volume over the last 35 days of treatment as measured by the alkaline hematin method. The primary endpoint will be referred to as responder rate and derived on the basis of the total MBL volume measured at the Week 24/EOT visit window taking into consideration the patient's compliance with return of feminine products and completion of the eDiary (see Section 7.3.2 and Section 7.3.4 for details).

7.3.1. Primary Efficacy Analysis

The following primary hypothesis for the primary efficacy endpoint will be tested:

Null hypothesis H_{01}: $\pi_R \leq \pi_P$ versus Alternative hypothesis H_{a1}: $\pi_R > \pi_P$

where π_R and π_P are the responder rates at Week 24/EOT for relugolix + E2/NETA (Group A) and placebo (Group C), respectively.

The treatment comparison between the relugolix + E2/NETA and the placebo will be analyzed using a Cochran-Mantel-Haenszel test statistic for proportions stratified by the Baseline mean MBL volume using the alkaline hematin method (< 225 mL versus ≥ 225 mL) and geographic region (North America versus Rest of World). The difference in responder rates between the relugolix + E2/NETA and placebo and its two-sided 95% CI will be estimated using stratum-adjusted Mantel-Haenszel proportions. The unadjusted responder rates and the difference in responder rates between the relugolix + E2/NETA and placebo groups and the corresponding two-sided 95% CI also will be provided. The study will be considered positive if the treatment effect for the primary endpoint is statistically significant with two-sided p-value < 0.05.

For the primary analysis, primary endpoint will incorporate the missing data handling rules described in Section 7.3.5.

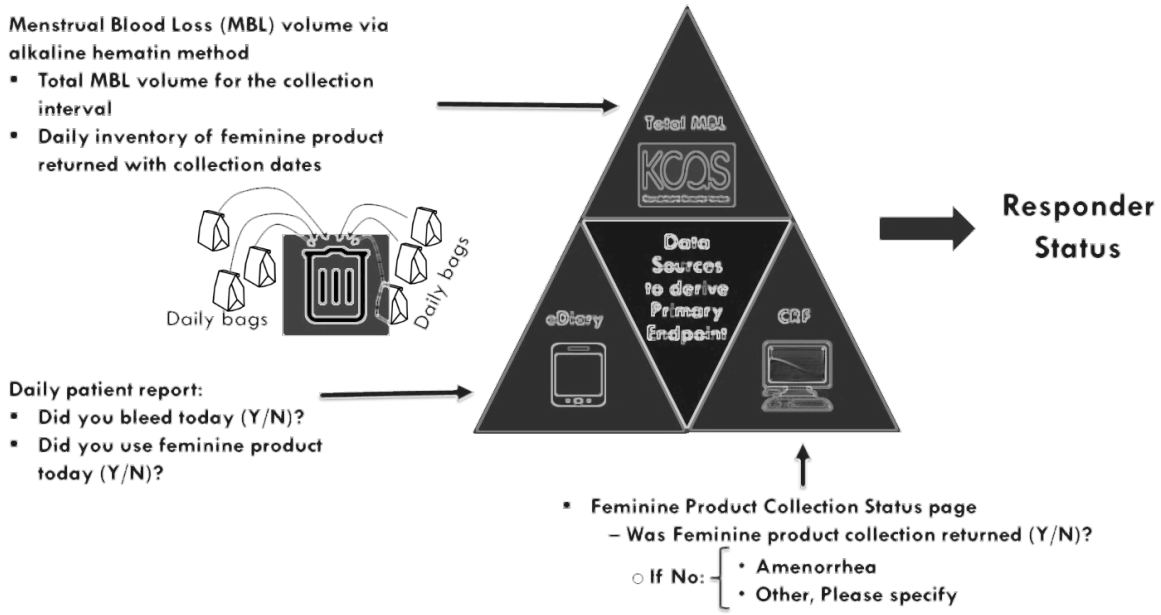
7.3.2. Data Sources Supporting Derivation of Responder Status

The data sources that will be used to support derivation of responder status, the primary endpoint, are depicted in Figure 2 below. They include:

- Menstrual blood loss volume determined by the alkaline hematin method;
- Daily patient report of bleeding (yes/no) and use of feminine product (yes/no) captured in the eDiary;
- The status of feminine product (FP) collection return (yes/no) recorded on the eCRF page at each visit with specific reasons captured when no product collection was returned.

The total MBL volume is reported from the analysis of FP returned for each collection interval. An inventory of days (with dates) for which FP was collected and returned is also available. This inventory is aligned with patients' reports of bleeding and FP use in the eDiary. The status of FP collection return, and specifically the reason for non-return of FP reported on the Feminine Product Collection eCFR page is used to support derivation of responder status (see Section 7.3.5 for details).

Figure 2: Data Sources Supporting Derivation of Primary Endpoint



Abbreviations: CRF = case report form.

7.3.3. Definitions Related to Menstrual Blood Loss

Menstrual Blood Loss Volume

All returned feminine products (validated, validated but unauthorized, or unvalidated products) collected at each visit will be analyzed by the alkaline hematin method to obtain the MBL volume. The MBL volume measured over the Week 24/EOT feminine product collection interval (up to 35 days prior to the last dose of treatment) will be used for analysis of the primary efficacy endpoint (see details below). The vendor, KCAS, reports when unauthorized feminine products (products not dispensed for use in the trial) have been returned. KCAS also reports whether the unauthorized products have previously been validated for their analysis. The report details MBL volumes for authorized, unauthorized but validated, and unauthorized and unvalidated products.

Validated Menstrual Blood Loss Volume

All returned feminine products collected at each visit, with the exception of unvalidated products, will be assessed by the alkaline hematin method to obtain the validated MBL volume. The validated MBL volume is derived from assessments of all returned validated feminine products (including validated and validated but unauthorized products) and will be used for sensitivity analysis.

Baseline Menstrual Blood Loss Volume

Baseline MBL volume is defined as the average MBL volume from the one or two consecutive screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method as follows:

For patients with MBL volume ≥ 160 mL during the screening period, the Baseline MBL volume is the last measurement collected before the first administration of study drug.

If the MBL volume is < 160 mL, the Baseline MBL volume is defined as the average of the MBL volume from the two screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method (see Figure 4-2 of the study protocol for details).

Week 24/EOT Feminine Product Collection Interval

To ensure collection of all feminine products used during that menstrual cycle, an interval of up to 35 days for measurement of the primary endpoint was selected to accommodate women who continue to have cyclic bleeding on study treatment and whose natural cycle was at the upper end of the normal cycle duration range. This method is consistent with that used during screening for collection of feminine products. Specifically, the feminine product collection interval at Week 24/EOT is driven by types of bleeding patterns experienced by the patients, as described below:

- For patients who continue to have cyclic bleeding, the length of the interval depends on the duration of the patient's natural cycle; this is consistent with the way the Baseline MBL volume was determined (eg, the interval ranging from approximately 21 to 35 days);
- Patients who report irregular, non-cyclic bleeding are instructed to collect and return all feminine product used between study visits, up to 35 days, as per the schedule of events;
- For patients who report amenorrhea on the feminine production collection eCRF page, an interval of last 35 days of treatment will be reviewed to ensure that reported amenorrhea is not due to incomplete collection.

For patients who are in the midst of an episode of cyclic bleeding at the time of the Week 24/EOT visit, the visit window may be extended up to 7 days after the last dose of study drug to ensure patients return all used feminine products over that bleeding episode.

Per protocol, all used feminine products are to be collected at each visit and returned for analysis using the alkaline hematin method. For patients who continue to have menstrual bleeding, study visits are timed such that the feminine products used in the entire menstrual bleeding cycle are collected in one container provided at each visit.

MBL Volume at Week 24/EOT

MBL volume at Week 24/EOT is defined as the MBL volume obtained from the feminine product returned over the Week 24/EOT feminine product collection interval, as described above. The MBL volume at Week 24/EOT will be used to derive the primary efficacy endpoint.

If a patient did not return feminine product over the last 35 days of treatment and reported amenorrhea on the feminine product return eCRF page, she will be considered as amenorrhoeic and her MBL volume will be assigned as 0 mL.

Feminine Product Return Rate at Week 24/EOT

To quantify degree of compliance with feminine product collection, the FPRR will be calculated based on the inventory of feminine product returned by day (dates) summarized on the Feminine Product Collection eCFR page (provided by the vendor, KCAS) and responses to the eDiary Question 4 regarding bleeding experience and Question 5 regarding the use of feminine product obtained for the corresponding eDiary window (see Table 5). Specifically:

- For those who returned feminine product at Week 24/EOT, the FPRR was calculated as the observed number of days with returned feminine products (based on the inventory of FP received by KCAS) divided by the expected number of days with bleeding and use of product as reported on the eDiary within the Week 24/EOT feminine product collection interval (as defined above).
- For those who did not return any feminine products:
  - If the reason was amenorrhea reported on the eCRF or if spotting/negligible bleeding was reported on the eCRF and confirmed by eDiary over the Week 24/EOT visit window, their FPRR will be set to 100% because the lack of menstruation obviates the need for feminine product collection.
  - Otherwise if the reason is any other, their FPRR was set to 0.

$$\text{FPRR} = \frac{\text{observed (No. of days with returned FP [per KCAS])}}{\text{expected (No. of days reported bleeding and use of FP [per eDiary])}} x100$$

Return of feminine products will be summarized in the CSR for Week 24/EOT visit.

7.3.4. Definition of Responder at Week 24/EOT

A responder at Week 24/EOT is defined as a patient who satisfies both the following:

- Had MBL volume of < 80 mL at Week 24/EOT;
- Had at least a 50% reduction from Baseline in MBL volume at Week 24/EOT.

The reduction from Baseline in MBL volume at Week 24/EOT will be calculated as the absolute change at Week 24/EOT in MBL volume from the Baseline MBL volume divided by the Baseline MBL volume.

Responder status at Week 24/EOT will be assessed based on the reported MBL volume at Week 24/EOT, in conjunction with treatment duration, compliance with feminine product collection, and compliance with eDiary entry over the same visit window (see Section 7.3.5 for details).

7.3.5. Derivation of Responder Status at Week 24/EOT and Missing Data Handling Rules

For the evaluation of primary endpoint, missing data handling rules will be implemented for deriving responder status at Week 24/EOT as described below. The following elements will be checked: duration of treatment exposure; compliance with feminine product collection against the eDiary, as measured by FPRR; compliance with eDiary entry, defined as the proportion of eDiary entry days over the length (days) of FP collection interval for Week 24/EOT visit; and reasons for no FP collection (as displayed in Table 7).

Patients with < 4 weeks of treatment who withdraw from the study prematurely due to lack of efficacy or withdraw from the study prematurely to undergo surgical intervention for uterine fibroids will be considered as non-responders.

All other patients will have their responder status determined as follows:

- For patients with a FPRR of 100%, responder status will be determined based on the observed MBL volume;
- For patients who had incomplete feminine product collection, with a FPRR of < 100%, responder status will be derived based on either imputed or observed MBL volume;
  - Those with an MBL volume ≥ 80 mL or < 50% reduction from Baseline will be considered as non-responders;
  - Those with an MBL volume < 80 mL and ≥ 50% reduction from Baseline will be imputed for partial or complete missing MBL volume (see Section 7.3.6 for details).
- For patients who did not return a feminine product collection, responder status will be determined depending on the reason reported on the Feminine Product Collection eCRF:
  - If the reason is reported as Amenorrhea, the last 35 days of treatment will be used to derive responder status:
    - If the Week 24/EOT interval was 35 days, then she will be considered as a responder;
    - If the Week 24/EOT interval was <35 days, the following supportive information will be used to derive responder status:
      - If a patient reported amenorrhea at the visit prior to Week 24/EOT, she will be defined as a responder;
      - If a patient did not report amenorrhea at the visit prior to Week 24/EOT, eDiary data from the prior visit interval will be reviewed to confirm whether the patient was amenorrheic for a total of 35 days.

- If the eDiary from the previous interval confirms amenorrhea, then the patient will be considered as a responder;
- Otherwise, MBL volume will be imputed.

- If the reason is Other and the specification describes spotting or negligible bleeding, responder status will be defined as follows:
  - The patient will be considered as a responder if it is supported by the eDiary data: the eDiary entry rate must exceed 70% and the patient must have reported no more than 5 total days of bleeding with product use and no more than 3 consecutive bleeding with product use over the collection interval.
  - If the eDiary entries did not confirm spotting or negligible bleeding, but the patient had at least 8 weeks of MBL volume data prior to the Week 24/EOT visit, her missing MBL volume will be imputed to determine responder status. Eight weeks of MBL volume data represents a reasonable minimum length of observation to justify imputation of the remaining data in assessing the effects of hormonal therapy.
  - Otherwise if the patient had < 8 weeks of MBL volume data, she will be considered as a non-responder;
- If the reason is any Other, the responder status will be derived as follows:
  - If the patient had at least 8 weeks of MBL volume data prior to the Week 24/EOT visit, her missing MBL volume will be imputed and her responder status will be based on the imputed MBL volume.
  - If the patient had < 8 weeks of MBL volume data, she will be considered as a non-responder.

Table 7: Derivation of Responder Status at Week 24/EOT and Missing Data Handling Rules – for Primary Analysis

Treatment Exposure	FP Collection (FPRR)	Observed MBL Volume	Reason for No FP Collection	Responder Status
< 4 weeks	N/A	N/A	N/A	Imputed as non-responder
≥ 4 weeks	100% FP Compliance	N/A	N/A	Based on the observed MBL volume
	<100% FP Compliance	MBL volume ≥ 80 mL or <50% reduction from Baseline	N/A	Imputed as non-responder based on the observed MBL volume
		MBL volume < 80 mL and ≥ 50% reduction from Baseline	N/A	**Based on the imputed MBL volume**
	No FP Collection	N/A	Reported "Amenorrhea"	Imputed as responder
			Reported "Spotting or negligible bleeding" and confirmed by eDiary[a]	Imputed as responder
			Reported "Spotting or negligible bleeding" although not confirmed by eDiary or any other reason, had at least 8 weeks of MBL volume data	**Based on the imputed MBL volume**
			The entries in the eDiary did not verify "Spotting or negligible bleeding" or any other reason and if had < 8 weeks of MBL volume data	Imputed as non-responders

Abbreviations: eDiary, electronic diary; FP, feminine product; EOT, end of treatment; MBL, menstrual blood loss; N/A, not available.

[a] Defined as those patients who meet the following criteria: eDiary entry rate > 70% and no more than 3 consecutive days and no more than 5 days of bleeding/spotting and use of feminine product reported on the eDiary over the Week 24/EOT visit window (see Table 5).

7.3.6. Mixed-Effects Model for Imputing Missing or Partially Missing MBL Volume at Week 24/EOT

For the primary analysis, patients with missing MBL volumes at Week 24/EOT will be identified per missing data handling rules as described above. For imputing missing data for the primary analysis, a mixed-effects model approach will be used, as the mixed-effects approach may better describe the effects of a hormonal treatment (such as suppression of the hypothalamic-pituitary-ovarian axis by GnRH antagonists).

Specifically, a mixed-effects model with repeated measures of MBL volumes at multiple time points (Weeks 4, 8, 12, 16, 20 and 24) will be fitted to predict percent change in MBL volume from Baseline (as a dependent variable) through the fixed-effects associated with covariates (ie, stratification factors of Baseline MBL volume and geographic region, visit, treatment, and visit by treatment interaction) and random effects (from the individual patients). In this model, an unstructured variance-covariance matrix is assumed for each patient.

See sample SAS codes below for illustration where PCHG_MBL is percent change in MBL volume from Baseline as a dependent variable, PID is patient identification number, BMBL is a randomization stratification factor (Baseline MBL < 225 vs ≥ 225), REGION is a randomization stratification factor (North America vs Rest of World), TRT is treatment group (relugolix + E2/NETA or Placebo), VISIT is visit time point (4, 8, 12, 16, 20, and 24 weeks) and TRT*VISIT is the visit by treatment interaction. The specification of type=UN implements unstructured variance-covariance matrix for an individual patient with multiple measures of MBL volumes.

```
proc mixed data=MBL_dataset method=REML covtest;
class PID BMBL REGION TRT VISIT;
model PCHG_MBL= BMBL REGION VISIT TRT VISIT*TRT/s outp=ufmi_mixed_p
covb;
repeated VISIT /type=UN subject=PID r;
lsmeans TRT/diff;
ods output SolutionF=mixparms CovB=mixcovb;
```

Applying this model over the observed longitudinal MBL volume data, the fixed-effects will be estimated and relationship of percent change in MBL volume from Baseline with the covariates will be characterized by the fitted model. From the fitted model, the percent change in MBL volume (whether missing or not) will be predicted for each patient at each visit and in a particular stratum. The imputed MBL volume will be obtained by first multiplying the imputed percent change with the individual patient's Baseline MBL volume to the difference, and then adding the Baseline BML volume to the difference.

The main reason for using percent change in MBL volume over reported MBL volume as a dependent variable in the mixed-effects model is that the percent change is part of the derivation of the primary endpoint. Secondly, the percent change is a normalized value adjusted for the Baseline value and less influenced by Baseline MBL volume, and therefore it is a better metric to describe the relationship of MBL volume reduction with hormonal treatment and to impute the missing volumes in a more robust fashion.

Since the purpose of using a mixed-effects model is imputing the missing MBL volumes identified at Week 24/EOT, the predicted MBL volumes at the corresponding Week 24/EOT visit will be used to determine responder status. For patients without the need for imputation, their responder status will be derived according to the algorithms laid out in Table 7. This imputation approach is consistent with the definition of responder at Week 24/EOT for the primary analysis.

7.3.7. Sensitivity Analyses

To assess the robustness of the primary analysis, the following sensitivity analyses of the primary endpoint will be conducted at Week 24/EOT.

7.3.7.1. Sensitivity Analysis 1

To assess the potential impact of unvalidated feminine product use, the primary endpoint will be analyzed as sensitivity analysis in a similar fashion to the primary analysis using the Week 24/EOT validated MBL volume (obtained from the validated or validated-but-unauthorized feminine products only and excluding unvalidated products).

7.3.7.2. Sensitivity Analysis 2

To assess the potential impact of missing data due to inadequate collection of feminine products, the primary endpoint will be analyzed with a sensitivity analysis using the missing data handling rules as described in Table 8 below where the observed MBL volume will be used to assess the responder status at Week 24/EOT when feminine product collection was incomplete. These rules differ from those used in the primary analysis in that no imputation will be implemented for patients with < 100% feminine product compliance and the reported MBL volume both < 80 mL and a ≥ 50% reduction from Baseline as highlighted in Table 8.

Table 8: Derivation of Responder Status at Week 24/EOT and Missing Data Handling Rules – for Sensitivity Analysis

Treatment Exposure	FP Collection (FPRR)	Observed MBL Volume	Reason for No FP Collection	Responder Status
< 4 weeks	N/A	N/A	N/A	Imputed as non-responder
≥ 4 weeks	100% FP Compliance	N/A	N/A	Based on the observed MBL volume
	< 100% FP Compliance	MBL volume ≥ 80mL or < 50% reduction from Baseline	N/A	Imputed as non-responder based on the observed MBL volume
		MBL volume < 80mL and ≥ 50% reduction from Baseline	N/A	**Based on the observed MBL volume**
	No FP Collection	N/A	Reported "Amenorrhea"	Imputed as responder
			Reported "Spotting or negligible bleeding" and confirmed by eDiary[a]	Imputed as responder
			Reported "Spotting or negligible bleeding" although not confirmed by eDiary or any other reason, had at least 8 weeks of MBL volume data	Based on the imputed MBL volume
			The entries in the eDiary did not verify "Spotting or negligible bleeding" or any other reason and if had < 8 weeks of MBL volume data	Imputed as non-responders

Abbreviations: eDiary, electronic diary; FP, feminine product; EOT, end of treatment; MBL, menstrual blood loss; N/A, not available.

[a] Defined as those patients who meet the following criteria: eDiary entry rate >70% and no more than 3 consecutive days and no more than 5 days of bleeding/spotting and use of feminine product reported on the eDiary over the Week 24/EOT visit window (see Table 5).

7.3.7.3. Sensitivity Analysis 3

To assess the potential impact of early discontinuation on the primary endpoint, the primary endpoint will be analyzed with a sensitivity analysis defining the patients' responder status as follows:

- Patients who discontinued study drug during the first 4 weeks for any reason or who discontinued study drug between Week 4 and Week 12 due to an adverse event, surgery or other intervention for heavy menstrual bleeding, reported lack of efficacy, or bleeding complaints will be considered as non-responders;
- All other patients will have their responder status defined using data from the Week 24/EOT assessment period using the last observation carried forward method.

7.3.7.4. Sensitivity Analysis 4

To assess the potential impact of the length and full exposure of the treatment, the primary endpoint will be analyzed for the Completers population as a sensitivity analysis. The Completers population is defined as patients in the mITT population who completed 24 weeks of study treatment.

7.3.7.5. Sensitivity Analysis 5

The primary endpoint will be analyzed on the Per-Protocol population as a sensitivity analysis, using the methods specified for the primary analysis (see definition of Per-Protocol population in Section 4.2.2).

7.3.7.6. Sensitivity Analysis 6

As a sensitivity analysis to the primary analysis using the mixed-effects model for imputing missing MBL volumes at Week 24/EOT, multiple imputation approach will be implemented as described below.

A multiple imputation method (Rubin, 1987; von Hippel, 2018) will be used to impute missing or partially missing MBL volume identified by the missing data handling rules (see Table 7 and Table 8) at Week 24/EOT as described in the following 5 steps. In this method, an arbitrary missing pattern will be assumed using Markov Chain Monte Carlo imputation to generate a monotone missing pattern for the observed longitudinal MBL volume values (including 0 mL if the patient has amenorrhea). Imputation will be performed separately by randomized treatment group (Sullivan, 2018), given the distinct bleeding patterns among the three treatment groups.

Normalizing transformations will be applied to the statistics estimated from each imputed dataset before the Rubin's combination rules can be applied (Ratitch, 2013). This combined estimation and statistical test will account for the additional variability due to imputation to provide a robust assessment of the treatment effect.

Step 1: Identifying patients with missing or incomplete MBL volume from the longitudinal MBL volume dataset as collected.

Step 2: Generating a monotone missing pattern using the Markov Chain Monte Carlo technique by imputing missing MBL volume measurements that are between non-missing results.

Step 3: Imputing the remaining missing values m = 100 times using a regression model; therefore, generating 100 complete longitudinal MBL volume datasets.

Note: if a patient missed Week 8 and prematurely discontinued study drug (eg, at Week 20) and MBL volume at Week 20 is missing or partially missing, MBL volume will be imputed for intermittent missing data at Week 8, Week 20 (EOT), and Week 24 due to discontinuation.

Step 4: Performing the same CMH test pre-specified for the primary endpoint analysis and estimating the responder rates for each arm using each of the 100 datasets based upon the MBL volume at Week 24/EOT.

Note: in the example above, the imputed MBL volume at Week 20 (EOT) will be used in the analysis, although MBL volume is imputed at Week 24.

Step 5: Combining the results from the 100 complete datasets to make inferences about the treatment effect on the responder rate.

7.3.8. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint comparing the relugolix + E2/NETA group versus the placebo group will be performed to assess whether treatment effects are consistent across clinically important subgroups. The odds ratio and its 95% CI based on a logistic regression model will be displayed in a forest plot for each subgroup. The logistic regression model will include treatment group, Baseline MBL volume value and geographic region as covariates. Subgroups will include, but will not be limited to, the subgroups outlined in Table 9.

Table 9: Planned Subgroup Analyses

Subgroup Name	Subgroup Level
Geographic region	North America vs Rest of World
Menstrual blood loss volume at Baseline (mL)	< 225 vs ≥ 225 < 120, 120 to < 160, 160 to < 225, ≥ 225
Age category (years)	< 40 vs ≥ 40 < 35, 35 to < 40, 40 to < 45, ≥ 45
Race	Black or African American vs Not Black or African American; Black or African American, White, Other
Volume of myoma at Baseline (cm^3)	< 25 vs ≥ 25
Volume of uterus at Baseline (cm^3)	< 300 vs ≥ 300
BMI (kg/m^2) at Baseline	< 30 vs ≥ 30 < 25, 25 to < 30, 30 to < 35, 35 to <40, ≥ 40
Maximum NRS score for uterine fibroid–associated pain at Baseline	< 4 vs ≥ 4
History of prior pregnancy	Yes/No

Abbreviations: BMI = body mass index; NRS = Numerical Rating Scale.

7.4. Secondary Efficacy Endpoints

Secondary efficacy variables include seven key secondary endpoints with alpha-protection and other secondary endpoints. All secondary efficacy endpoints and analyses are summarized in Appendix 1.

The treatment effect of relugolix + E2/NETA (Group A) compared to placebo (Group C) will be tested for the alpha-protected secondary endpoints using a gate-keeping procedure (see Section 7.4.1).

Comparative statistics (p-values, 95% CIs for differences) will be provided for treatment comparison of the relugolix + E2/NETA group with the placebo group for all other secondary efficacy endpoints. Treatment difference between the relugolix + delayed E2/NETA group and the placebo group will be formally tested only for the primary efficacy endpoint. There will be no statistical testing for treatment differences between the relugolix groups (relugolix + E2/NETA group against relugolix + delayed E2/NETA group) for any efficacy endpoint (see Section 7.4.2).

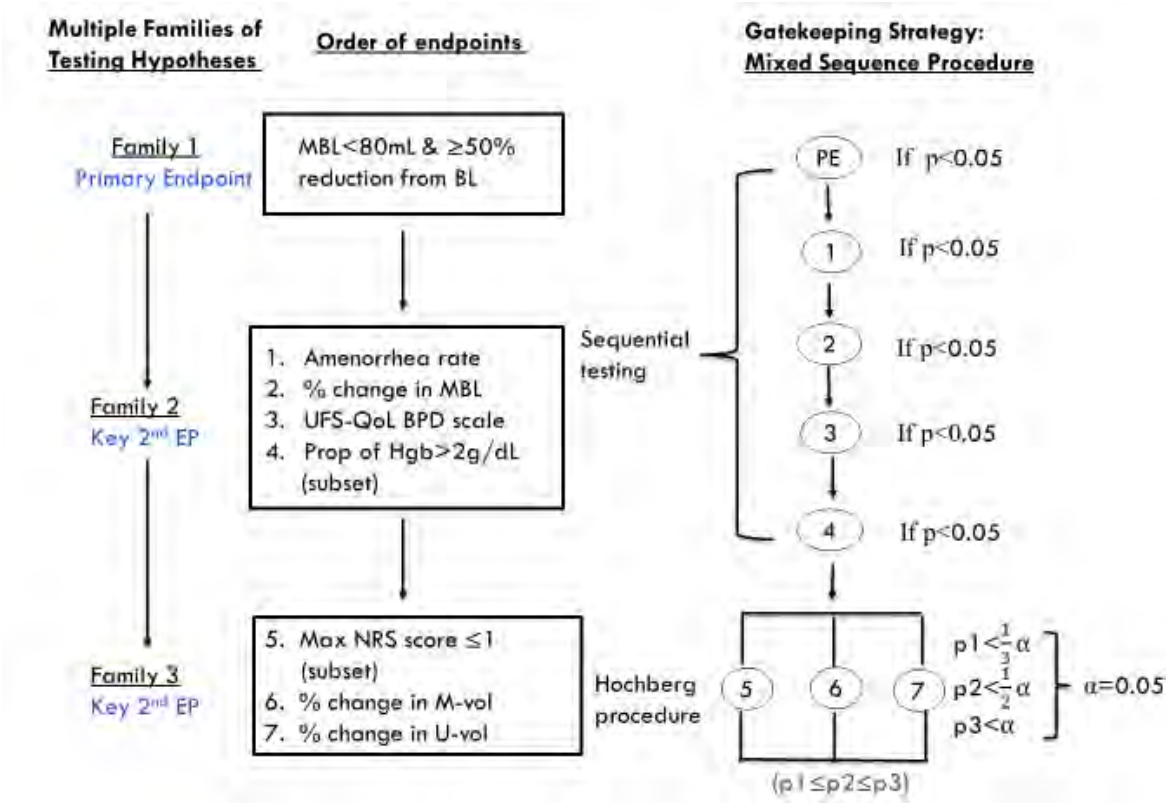
7.4.1. Key Secondary Efficacy Endpoints with Alpha-Protection

For testing whether relugolix + E2/NETA (Group A) is statistically significantly superior to placebo (Group C) for the primary efficacy endpoint as well as the seven key secondary endpoints listed below, a gate-keeping mixed sequence testing procedure will be applied to maintain the family-wise type I error rate. Under this testing procedure, the primary endpoint

will be tested first at a 2-sided 0.05 significance level. If the p-value for primary endpoint is < 0.05, the seven key endpoints listed below will be tested sequentially in the order depicted in Figure 3 (LIBERTY 1) and Figure 4 (LIBERTY 2).

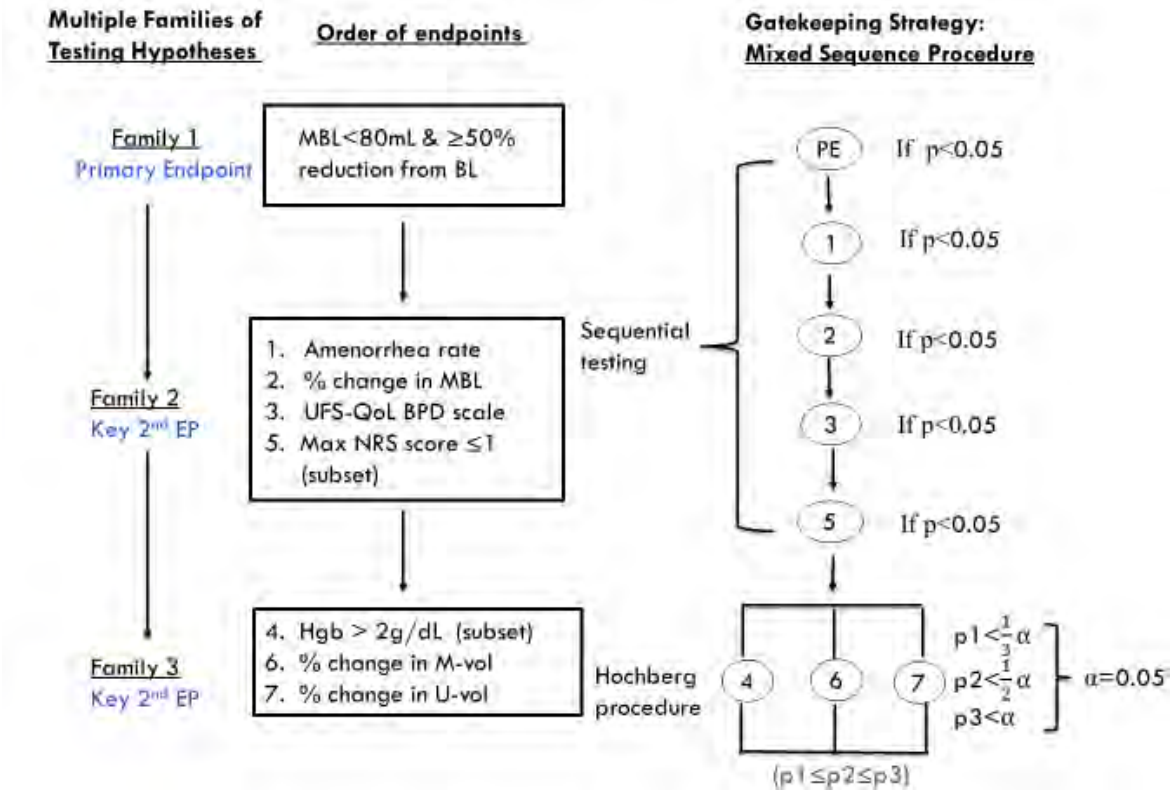
For the relugolix + E2/NETA group to be considered statistically superior to the placebo group on a secondary endpoint, the two-sided p-value must be < 0.05 for that secondary endpoint and for all higher-ranking secondary endpoints, as well as for the primary endpoint. If the two-sided p-value is < 0.05 for the fourth endpoint (proportion of women with hemoglobin ≤ 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24 for LIBERTY 1; proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid-associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization for LIBERTY2), the remaining three endpoints (the fifth, sixth, or seventh) will be tested using the Hochberg step-up procedure.

Figure 3: Mixed Sequence Testing Procedure for Primary and Key Secondary Endpoints in LIBERTY 1



Abbreviations: BPD = Bleeding and Pelvic Discomfort; EP = endpoint; Hgb = hemoglobin; max = maximum; MBL = menstrual blood loss; M-vol = myoma volume; NRS = Numerical Rating Scale; PE = primary endpoint; Prop = proportion; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort; U-vol = uterine volume.

Figure 4: Mixed Sequence Testing Procedure for Primary and Key Secondary Endpoints in LIBERTY 2



Abbreviations: BPD = Bleeding and Pelvic Discomfort; EP = endpoint; Hgb = hemoglobin; max = maximum; MBL = menstrual blood loss; M-vol = myoma volume; NRS = Numerical Rating Scale; PE = primary endpoint; Prop = proportion; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort; U-vol = uterine volume.

From the Hochberg procedure, the p-values will be calculated for the three endpoints (5, 6, and 7) and ranked from the smallest to the largest. The endpoint corresponding to the largest p-value gets tested first. If the p-value is < 0.05, then no further testing will occur, and it will be concluded that all three endpoints are positive. Otherwise, the endpoint corresponding to the second largest p-value will be tested. If the p-value is < 0.025, then no further testing will occur, and it will be concluded that the endpoints corresponding to the middle and smallest p-values are positive. Otherwise, the endpoint with the smallest p-value will be tested. If the p-value is < 0.0167, no further testing will occur, and it will be concluded that only the endpoint with the smallest p-value is positive. Otherwise, all three endpoints did not pass the statistical significance criterion at 0.05 level.

The seven key secondary efficacy endpoints are as follows:

1. Proportion of women who achieve amenorrhea over the last 35 days of treatment;
2. Percent change from Baseline to Week 24 in MBL volume;

3. *Change from Baseline to Week 24 in Bleeding and Pelvic Discomfort Scale score as measured by the UFS-QoL Symptom Severity Scale (Q1, Q2, Q5);*
4. *Proportion of women with a hemoglobin ≤ 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24*
5. *Proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;*
6. Percent change from Baseline to Week 24 in uterine fibroid volume;
7. Percent change from Baseline to Week 24 in uterine volume.

For key secondary efficacy endpoints (1, 4, and 5) that are evaluating proportions, treatment comparisons will be performed using a stratified Cochran-Mantel-Haenszel test with the randomization stratification factors as strata. Point estimates and 2-sided 95% CIs for treatment differences in proportions will be provided.

For key secondary endpoint 4, an increase in hemoglobin of 2g/dL is considered clinically meaningful, because it corresponds to approximately the same increase as that expected after a transfusion of ~ 2 units of packed red blood cells (Man, 2016; Bachowski, 2017).

For deriving the key secondary endpoint 5 (proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid-associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization), the patient subset and Week 24/EOT maximum value are determined as follows.

Because patients were asked to begin eDiary entries after returning the first collection of feminine products, the number of eDiary entries made during screening varies with the duration of screening for each patient. Some patients required only one collection to be randomized, whereas others required as many as four collections to confirm eligibility.

Once the qualifying menstruation was completed and the patient qualified for randomization based upon resulting MBL volume(s), the recording of patient's NRS scores for screening phase will be ended and the number of pain score days at Baseline can be as short as 7 days or as long as 70 days prior to randomization. If a patient meets the subset definition (maximum NRS score ≥ 4 at Baseline) over a portion of the screening days (eg, 7-70 days), she will also meet the subset definition on the entire 35 days interval.

Since the maximum NRS value is used to determine inclusion into the subset rather than an average NRS value, the variable number of days for inclusion of patients has no major impact on determining patient subset. To ensure robust estimate of response, the minimum number of non-missing daily pain scores required to calculate the maximum score at Week 24/EOT is at least 28 days (80% of the last 35 days of treatment) of pain scores recorded in the e-Diary entry.

The primary analysis of key secondary endpoint 5 will be analyzed for the subset of women who have a maximum pain score ≥ 4 during the 35 days prior to randomization and who have at least 28 days (80% of the last 35 days of treatment) of pain scores recorded in the e-Diary at Week 24/EOT. In addition, a sensitivity analysis will be conducted on the subset of women who have

a maximum pain score ≥ 4 during the 35 days prior to randomization without restricting number of days of pain scores recorded in the e-Diary.

The analysis for endpoint 5 (proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid-associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization) will also be performed using NRS scores reported on eDiary during menstrual and non-menstrual days.

For key secondary efficacy endpoints (6 and 7) evaluating percent change from Baseline in uterine fibroid volume and uterine volume that are measured only at Week 24, an analysis of covariance (ANCOVA) model will be used to assess treatment effect with treatment, randomization stratification factors and Baseline value as covariates.

For key secondary efficacy endpoints (2 and 3) evaluating the change (absolute or % change) from Baseline to Week 24, treatment comparisons will be performed using a mixed model repeated measures approach with treatment, visit, randomization stratification factors and treatment by visit interactions included as fixed effects and random effects (from the individual patients). In this model, an unstructured variance-covariance matrix is assumed for each patient.

7.4.2. Other Secondary Efficacy and Exploratory Endpoints

The following describes the analysis methods for other secondary efficacy endpoints and exploratory endpoints. There are three types of analyses corresponding to the three types of endpoints (time-to-event, continuous and binary) (see Appendix 1 for details).

Time-to-Event Endpoint

For time to achieving an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume (as an event), time to event will be defined as weeks from date of first dose of study drug to response (event) based on the MBL volume as assessed by the alkaline hematin method. The missing data handling rules described in Section 7.3.5 for deriving responder status at Week 24/EOT will be applied similarly at Weeks 8, 12, 16, and 20. Patients without an event will be censored at the last assessment date prior to the last dose of the study drug. Kaplan-Meier methods will be used to describe the time to event distributions. A log-rank test stratified by the randomization stratification factors using the proportional hazard model (p-value from score test) will be used to compare relugolix + E2/NETA to placebo. Randomization stratification factors will be used to stratify inferential testing.

Continuous Endpoints

For endpoints evaluating the change (absolute or percent change) from Baseline to Week 24, treatment comparisons will be performed using a mixed model repeated measures approach with treatment, randomization stratification factors, visit, and treatment by visit interactions included as fixed effects. The Baseline value will be included as a covariate, and an unstructured variance-covariance matrix will be assumed. Calculation of the dependent variable (change from Baseline) for each patient at each visit will be calculated based on the visit windows specified in Section 4.3.5. Based on this model, the least squares mean at Week 24 will be compared between treatment groups and summarized along with the corresponding 95% CIs for treatment difference. In addition, summary statistics (mean change or mean % change) will be graphically presented as appropriate.

Binary Endpoints

For endpoints evaluating proportions, treatment comparisons will be performed using a stratified Cochran-Mantel-Haenszel test as appropriate with the randomization stratification factors as strata. Point estimates and 2-sided 95% CIs for treatment differences in proportions will be provided.

Descriptive statistics (point estimates and corresponding 95% CIs) will be provided by treatment group and visit as appropriate for all secondary endpoints.

Responder rate by visit (at Week 4, Week 8, Week 12, Week 16, and Week 20) will be derived in a similar fashion to the derivation of responder rate at Week 24/EOT. The missing data handling rules described in Section 7.3.5 for deriving responder status at Week 24/EOT will be applied similarly at Weeks 4, 8, 12, 16, and 20.

7.4.3. Derivation of Amenorrhea-Related Endpoints

Determination of Amenorrhea

Rules for determining amenorrhea in the treatment period is defined as those who meet 1 of the following requirements for 2 consecutive visits (approximately 56 consecutive days). Patients will be deemed to have amenorrhea during a visit window according to the following rules:

- No feminine product returned due to reported amenorrhea in 2 consecutive visits

OR

- No feminine product returned due to other reasons or feminine product collection with a negligible observed MBL volume coupled with other data indicating infrequent non-cyclic bleeding/spotting as described in Table 10.

Missing responses for menstrual bleeding questions in the eDiary will be treated as “No Bleeding” if eDiary compliance rate is > 70%.

Table 10: Rules for Determining Amenorrhea by Visit

Feminine Product Collection (KCAS) [a]	Supporting Data	
	Menstruation Status eCRF	**eDiary**
No feminine product collection due to reported amenorrhea	No menses start/stop dates reported	N/A
No feminine product collection due to other reasons	Per instructions for non-cyclic bleeding patterns, menses start date is reported but no menses stop date reported	• Data indicating infrequent, non-cyclic bleeding/spotting defined as bleeding/spotting with feminine product use for no more than 3 consecutive days and no more than 5 days bleeding total per visit window • eDiary entry rate > 70%
Feminine product collection with negligible observed MBL volume defined as <5 mL	Full or partial menses start and stop dates	• Data indicating infrequent, non-cyclic bleeding/spotting defined as bleeding/spotting with feminine product use for no more than 3 consecutive days and no more than 5 days bleeding total per visit window • eDiary entry rate > 70%

Abbreviations: eCRF, electronic case report form; eDiary, electronic diary; MBL, menstrual blood loss; N/A = not applicable.
[a] There is no requirement for feminine product return rate, as the determination of amenorrhea is based on the eDiary response.

Amenorrhea During the Last 35 Days of Treatment

Patients with amenorrhea over the last 35 days of treatment are defined as those who meet the definition of amenorrhea. A patient's amenorrhea status will also be summarized at Weeks 8, 12, 16, and 20. If a patient does not return for her Week 24/EOT visit, the eDiary responses for the last 35 days of treatment will be evaluated. If the criteria for infrequent, non-cyclic bleeding or spotting as indicated in Table 10 is met and the criteria for amenorrhea is met at the prior visit, the patient will be categorized as amenorrheic at Week 24/EOT. At all other timepoints, patients who do not return for a specific visit will be assigned as not amenorrheic at that visit.

Time to Amenorrhea

Time to amenorrhea is defined as the weeks from date of first dose of study drug to the start date of the amenorrhea window. Time to sustained amenorrhea will also be estimated and plotted using the Kaplan-Meier method.

The start date of amenorrhea is defined as the last feminine product collection date prior to start of amenorrhea. For example, if a patient's feminine product was collected at her Week 4 visit and MBL volume for this cycle did not indicate amenorrhea, and the patient reported amenorrhea on Week 8 and 12 visits, then time to start amenorrhea will be defined as starting on the date of feminine product collection for Week 4. Patients who are determined to have amenorrhea at Week 4 and Week 8 will use their Week 4 feminine product collection date as start date of amenorrhea. Patients without an event will be censored at the last assessment date prior to the last dose of the study drug.

Sustained Amenorrhea Rate by Visit

A patient's sustained amenorrhea status will be summarized at Weeks 8, 12, 16, 20, and 24, based on her time to achieving and maintaining amenorrhea until the date of last study drug dose as shown in Table 11. For example, at Week 8, a patient is considered to have achieved sustained amenorrhea status if her amenorrhea started before Week 8 and was observed every visit thereafter until the last dose of the study treatment. The proportion of patients with sustained amenorrhea will be summarized by visit. If a patient met the criteria for sustained amenorrhea but discontinues from the study, this subject's amenorrhea status will be carried forward to the Week 24 visit.

Table 11: Sustained Amenorrhea Rate by Visit

	Amenorrhea Window	
Time Point	Start	End
Week 8	Determined amenorrhea at Week 4	Amenorrhea observed at Week 8 and was observed at every visit thereafter until and including the last dose of study treatment
Week 12	Determined amenorrhea at Week 8	Amenorrhea observed at Week 12 and was observed at every visit thereafter until and including the last dose of study treatment
Week 16	Determined amenorrhea at Week 12	Amenorrhea observed at Week 16 and was observed at every visit thereafter until and including the last dose of study treatment
Week 20	Determined amenorrhea at Week 16	Amenorrhea observed at Week 20 and was observed at every visit thereafter until and including the last dose of study treatment
Week 24	Determined amenorrhea at Week 20	Amenorrhea observed at Week 24

7.4.4. Derivation of Patient-Reported Outcome

7.4.4.1. Numerical Rating Scale Score for Pain Associated with Uterine Fibroids

Patients completed daily eDiaries including assessment of uterine fibroid-associated pain by the Numerical Rating Scale (NRS). Patients rated their worst pain in the last 24 hours caused by their uterine fibroids on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The maximum NRS score for pain at Week 24/EOT is calculated as the maximum NRS score during the last 35 days on study treatment. If any NRS scores for pain during the last 35 days on study treatment are missing, the maximum score will be calculated as the maximum of all non-missing scores. Baseline NRS score for uterine fibroid-associated pain is defined as the maximum NRS score from the 35 days of data collected prior to randomization.

Proportion of women who achieve a *maximum* NRS score for pain associated with uterine fibroids over the last 35 days of treatment that is at least a 30% reduction from Baseline will be summarized in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization (subset). In addition, for the subset, mean maximum NRS scores will be provided by treatment and visit. Maximum NRS score for each patient at a visit is defined as the highest NRS score reported in the visit window specified in Table 2.

7.4.4.2. UFS-QoL Score

Calculation of UFS-QoL Symptom Severity Scale Score

To calculate the Symptom Severity Scale score, a summed score is created for the items listed below and then the formula below the table is used to transform raw scores to a normalized score with a range of possible values from 0 to 100. This provides Symptom Severity Scale scores, where higher scores are indicative of greater symptom severity and lower scores indicate lower symptom severity.

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Symptom Severity	Sum 1 – 8	8, 40	32

Formula for Transformation of Symptom Severity Raw Scores ONLY:

Transformed Score = [(Actual raw score – lowest possible raw score)/(Possible raw score range)] * 100

Calculation of UFS-QoL Bleeding and Pelvic Discomfort Scale Score

The UFS-QoL Bleeding and Pelvic Discomfort (BPD) Scale has been derived from the UFS-QoL Symptoms Scale; the derivation and validation of this new scale can be found in Appendix 3. The new scale consists of the following three symptoms proximal to uterine fibroids:

- Heavy bleeding during your menstrual period (Q1)
- Passing blood clots during your menstrual period (Q2)
- Feeling tightness or pressure in your pelvic area (Q5)

To calculate the score for the BPD Scale, a summed score of the items listed below is created and then the formula below the table is used to transform the raw score to a normalized score. This provides BPD Scale scores, where higher score values are indicative of greater symptom severity and lower scores will indicate minimal symptom severity (high scores = bad).

Sub-Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Q1, Q2 and Q5	Sum 1,2,5	3, 15	12

Formula for Transformation of BPD Raw Scores ONLY:

Transformed Score = [(Actual raw score – lowest possible raw score)/(Possible raw score range)] * 100

On the basis of transformed score for BPD Scale, change from Baseline in the transformed score for BPD Scale at Week 24 will be defined as an alpha-protected key secondary endpoint comparing the relugolix + E2/NETA group with the placebo group. The proportion of patients who are responders (defined as meeting a meaningful change threshold from Baseline in the BPD Scale) at Week 24 on the transformed score for the BPD Scale will be compared between the two treatment arms (the relugolix + E2/NETA group with the placebo group) using a stratified Cochran-Mantel-Haenszel test, as appropriate. The proposed responder threshold is a 20-point change. Details in the determination of the meaningful change in the BPD Scale can be found in Appendix 4.

As a descriptive assessment on robustness of the responder analysis, a plot of the cumulative distribution function (CDF) will be provided for each treatment group to display the change from Baseline to Week 24 in the transformed score for BPD Scale on the x-axis and cumulative percentage of patients experiencing up to that change on the y-axis.

Calculation of Other UFS-QoL Scale Scores and UFS-QoL Total Score

For the other UFS-QoL scales (concern, activities, revised activities, energy/mood, control, self-conscious, and sexual function), a summed score of the items listed below is created for each individual scale. To calculate the UFS-QoL total score, the values for each individual scale are summed. Using the formula below the table, all raw scores are transformed to normalized scores. Higher scores are indicative of better health-related quality of life (high = good).

For endpoints evaluating a single question, the raw score is used in the analysis. The activity and revised activity domain scores will be summarized by treatment group.

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Concern	9+15+22+28+32	5, 25	20
Activities	10+11+13+19+20+27+29	7, 35	28
Revised activities	11+13+19+20+27	5,25	20
Energy/mood	12+17+23+24+25+31+35	7, 35	28
Control	14+16+26+30+34	5, 25	20
Self-conscious	18+21+33	3, 15	12
Sexual function	36+37	2, 10	8
HRQL TOTAL	Sum of 6 Subscale Scores[a]	29, 145	116

Abbreviations: HRQL, health-related quality of life.

[a] HRQL Total includes following scales: concern, activities, energy/mood, control, self-conscious, and sexual function.

Formula for Transformation of Raw Scores of Other Scale Scores ONLY:

Transformed Score = [(Highest possible score – Actual raw score)/(Possible raw score range)] * 100

For revised activities, the proportion of patients who are responders (defined as meeting a meaningful change from Baseline in the revised activity score) at Week 24 will be analyzed similarly to that for the change in BPD Scale score between the two treatment arms (relugolix + E2/NETA and placebo). The proposed responder threshold is a 20-point increase. Details of the determination of the meaningful change in the Revised Activities Scale score can be found in Appendix 5.

Missing Items

For any scale analyses, if < 50% of the scale items are missing, the scale should be retained using the mean scale score of the items present. If ≥ 50% of the items are missing, no scale score should be calculated; the subscale score will be considered missing.

7.4.4.3. Patient Global Assessment

The PGA for function and symptoms will be evaluated using a 5-point response scale (eg, absent, mild, moderate, severe, and very severe). To calculate change from Baseline to Week 24, the following numerical scores will be assigned to each response level:

Response Scale (Function)	Response Scale (Symptoms)	Numerical Score
No limitation at all	Not severe	1
Mild limitation	Mildly severe	2
Moderate limitation	Moderately severe	3
Quite a bit of limitation	Very severe	4
Extreme limitation	Extremely severe	5

For each item, the count and proportion of improvement by level or at least one level will be tabulated by treatment group and by visit. The denominator for the proportion will be based on the number of patients who provided non-missing responses to the items.

7.4.4.4. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire items 3 and 4 will be evaluated using the 5-point response scales (Not at all, Slightly, Moderately, Quite a bit, and Extremely) to assess level of improvement from Baseline to Week 24.

For each item, the count and proportion of improvement by level will be tabulated by treatment group and by visit. The denominator for the proportion will be based on the number of patients who provided non-missing responses to the items.

7.5. Exploratory Efficacy Endpoints

The following exploratory endpoints will be assessed for both comparisons the relugolix + E2/NETA group with the placebo group and the relugolix + delayed E2/NETA group with the placebo group:

- Change from Baseline to Week 24 in the EQ-5D-5L Scale score
- Change from Baseline to Week 24 in EQ-5D-5L visual analogue score.

7.5.1. Exploratory Efficacy Analyses

Analysis methods previously described for primary and secondary efficacy endpoint analyses will be used for the analysis of these endpoints.

8. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Plasma relugolix, plasma NET, and serum E2 trough concentrations will be listed and summarized by study, treatment group (Group A, B, or C), and visit.

Serum pharmacodynamic data (LH, FSH, E2, and progesterone) will be listed and summarized using descriptive statistics (including raw and change from Baseline) by study, treatment group (Group A, B, or C), and visit.

For pharmacodynamic assessment, the number and percentage of patients with individual E2 concentration values < 10 pg/mL, 10 to < 20 pg/mL, 20 to < 50 pg/mL, and ≥ 50 pg/mL and individual progesterone concentration values < 1 ng/mL, 1 to 5 ng/mL, and ≥ 5 ng/mL will be summarized by treatment group (Group A, B, or C) and visit.

Scatter plots with LOESS smoothing lines for MVT-601-3001 and MVT-601-3002 separately will be used to examine the relationship between mean plasma relugolix trough concentration at the given time point (collected between 18 and 30 hours after the previous dose) and the following pharmacodynamic concentrations:

- Week 12 serum LH, FSH, E2, and progesterone (separately for Groups A and B);
- Week 24 serum LH, FSH, E2, and progesterone (separately for Groups A and B, and Groups A and B combined).

In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes. The analysis plan for population PK and exposure-response analyses will be specified in a separate document.

9. SAFETY ANALYSES

Unless otherwise specified, safety analyses will be conducted using the safety population according to the treatment received by the patients.

9.1. Adverse Events

Adverse events will be collected from the time of the first dose of study drug through the safety follow up visit approximately 30 days after the last dose of study drug (the end of treatment period), or the date of initiation of another investigational agent or hormonal therapy or surgical intervention or entering extension study, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to study drug.

The severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term and system organ class using MedDRA 22.0 or higher.

A treatment-emergent adverse event is defined as any adverse event that occurs after administration of the first dose of study drug.

Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. Adverse events occurring prior to administration of any study drug will be listed and flagged in by-patient listings.

The following tabular summaries that include the number and percentage of patients will be provided:

- Overview of adverse events;
- All adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;
  - Study drug-related per investigator by SOC and PT;
  - By time to onset, SOC and PT;
- Grade 3 or above adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - Study drug-related per investigator by SOC and PT;
- Grade 2 or above adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;

  - Study drug-related per investigator by SOC and PT;
- Adverse events leading to study drug withdrawal;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Adverse events leading to dose interruption;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Adverse events resulting in fatal outcome;
  - By decreasing frequency of PT;
- Serious adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;
  - By SOC, PT, and relationship to study drug;
- Adverse events of clinical interest (ALT or AST ≥ 3 x ULN);
  - By SOC, PT, and maximum severity;
  - By decreasing frequency of PT.

Additionally, adverse event categories defined in Table 12 will be summarized by decreasing frequency of PT.

9.1.1. Relationship to Study Drug

Adverse events will be classified as "related" to study treatment if the relationship was rated by the investigator as possibly related or probably related. Adverse events related to any study drug (relugolix or placebo and E2/NETA or placebo) will be considered as related to study drug.

9.1.2. Severity of Adverse Event

Grade 2 or above adverse events will be summarized by SOC, PT, and/or maximum severity, relationship to study treatment.

9.1.3. Serious Adverse Event

Serious adverse events will be summarized by SOC, PT, and/or maximum severity, relationship to study treatment.

The data handling conventions for and the definition of a serious adverse event are discussed in this section. All deaths during the study, including the post treatment follow-up period, and deaths that resulted from a process that began during the study, should be included in the

analysis. For more details, deaths occurring during the following time periods or under the following conditions should be considered:

- Deaths occurring during participation in any study, or during any other period of drug exposure
- Deaths occurring after a patient leaves a study, or otherwise discontinues study drug, whether or not the patient completes the study to the nominal endpoint, if the death:
  - Is the result of a process initiated during the study or other drug exposure, regardless of when it actually occurs; or
  - Occurs within a time period that might reflect drug toxicity for a patient leaving a study or otherwise discontinuing drug. For drugs with prompt action and relatively short elimination half-lives, 4 weeks is a reasonable time period. For drugs with particularly long elimination half-lives or drug classes with recognized potential to cause late occurring effects, deaths occurring at longer times after drug discontinuation should be evaluated.

9.1.4. Adverse Event Leading to Withdrawal of Study Drug

Adverse events leading to withdrawal of study drug are those adverse events collected from the adverse event CRF pages with “drug withdrawn” as the action taken with study drug.

Adverse events with “drug withdrawn” as action taken due to any one of the components of study drug will be considered as leading to withdrawal of study drug.

9.1.5. Adverse Events Leading to Dose Interruption

Adverse events leading to dose interruption are those adverse events collected from the adverse event CRF pages with “drug interrupted” as their action taken with study drug.

Adverse events with “drug interrupted” as action taken due to any one of the components of study drug will be considered as leading to dose interruption.

9.1.6. Adverse Events Resulting to Fatal Outcome

Adverse events resulting in a fatal outcome are those adverse events collected from the adverse event pages with “fatal” as their outcome.

The fatal events, if any, will be provided in a by-subject listing.

9.1.7. Adverse Event Categories

In addition, adverse event categories defined in Table 12 will be summarized by decreasing frequency of PT under each safety population. Incidence of vasomotor symptoms by 12 weeks will be compared between relugolix Group A and relugolix Group B. Comparative statistics (such as p-values, 95% CIs, risk ratio) will be provided. Vasomotor symptoms throughout the studies will be summarized by SOC, PT, and maximum severity.

Table 12: Constitution of Adverse Event Categories

Category	Search Criteria
Bone health events	Osteoporosis/Osteopenia SMQ (broad) Fracture (custom SMQ): All preferred terms including the term "fracture," excluding "Tooth fracture" and "Fracture of penis"
Hepatic disorders	Drug-related hepatic disorders – comprehensive SMQ (narrow)
Metabolic disorders	Dyslipidemia SMQ (broad) Hyperglycemia/new onset diabetes mellitus SMQ (narrow)
Vasomotor symptoms	The following 5 preferred terms will be included: Hyperhidrosis; Feeling hot; Hot flush; Night sweats; Flushing
Mood disorders	MedDRA Depression and Suicide/Self-Injury SMQ (broad)

Abbreviations: HLT, High-Level Term; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardised MedDRA Query.

9.2. Laboratory Data

Laboratory parameters, including chemistry and hematology panels, specified as per protocol, and collected from the central laboratory will be tabulated and presented in by-patient listings. Urinalysis and hepatitis virus serological test results will be provided in by-patient listing only.

The National Cancer Institute CTCAE Grading Scale with numeric component will be used to categorize toxicity grade for laboratory parameters (CTCAE v5.0, dated 17 Nov 2017). Parameters that have criteria available for both low and high values (eg, hypercalcemia for a high value of calcium and hypocalcemia for a low value of calcium) will be summarized for both criteria (low and high). Patients will only be counted once for each criterion. The same patient can be counted for both criteria if she has laboratory values meeting each criterion. Shift tables will be provided for each gradable parameter to summarize Baseline toxicity grade versus worst post-Baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the Baseline versus worst post-Baseline results.

Boxplots of laboratory values over time will be plotted for key laboratory parameters. These laboratory parameters include, but are not limited to, hematology (hemoglobin, platelets,

leukocytes, neutrophils), creatinine, glomerular filtration rate, and hepatic function panel (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin).

The change from Baseline to each post-Baseline study visit will be presented by treatment group for each laboratory test in both tables and figures.

The number and proportion of patients with liver test elevations will be presented by treatment group. Liver test elevations are assessed by using post-Baseline results for ALT, AST, ALP, and total bilirubin based on the definitions presented in Table 13.

Table 13: Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN - < 3xULN ALT or AST ≥ 3x to < 5x ULN ALT or AST ≥ 5x to < 8x ULN ALT or AST ≥ 8x to < 10x ULN ALT or AST ≥ 10 to < 20x ULN ALT or AST ≥ 20x ULN
Total bilirubin	Total bilirubin > 2 × ULN
ALT or AST and total bilirubin	ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	ALT or AST ≥ 3 x ULN + total bilirubin > 2 × ULN + ALP < 2 × ULN

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

The number and percentage of patients with concurrent (defined as measurements on the same day) ALT or AST ≥ 3 times ULN and total bilirubin > 2 times ULN will also be presented.

9.3. Other Safety Analyses

9.3.1. Electrocardiograms

ECG interval results and changes from Baseline will be summarized descriptively for each scheduled visit in both tables and figures using data provided by and read by central reading.

A categorical analysis of corrected QT interval using Fridericia's calculation (QTcF) intervals will also be performed for each scheduled visit and for the maximum post-Baseline value. The number and percentage of patients in each QTcF interval category (< 450 msec, 450 to 480 msec, 481 to 500 msec, and > 500 msec) will be summarized. Categories of changes from Baseline (≥ 30 msec and ≥ 60 msec) will be summarized as well.

ECG intervals will be presented in by-patient listing. Overall ECG assessments performed by local reading will also be listed.

9.3.2. Visual Acuity

Visual Acuity Score at Baseline and at each scheduled post-Baseline assessment time point will be presented in a by-patient listing.

9.3.3. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and BMI will be summarized at Baseline and each subsequent scheduled assessment by treatment group. Change from Baseline will be calculated and presented for each parameter at all scheduled post-Baseline assessment time points in both tables and figures. All vital sign data will also be provided in by-patient listings.

Potentially clinically significant abnormalities in vital signs are defined in Table 14, and they will be summarized by using post-Baseline values that meet the defined criteria. Potentially clinically significant abnormalities will also be flagged in by-patient listings.

Table 14: Categories of Potentially Clinically Significant Abnormalities in Vital Signs

Parameter	Category
Systolic blood pressure	≥ 140 mmHg ≥ 180 mmHg
	≤ 90 mmHg
	Increase of ≥ 20 mmHg from Baseline Decrease of ≥ 20 mmHg from Baseline
Diastolic blood pressure	≥ 90 mmHg ≥ 105 mmHg
	≤ 50 mmHg
	Increase of ≥ 15 mmHg from Baseline Decrease of ≥ 15 mmHg from Baseline
Heart rate	≥ 120 bpm
	< 45 bpm
	Increase of ≥ 15 bpm from Baseline Decrease of ≥ 15 bpm from Baseline

Abbreviations: bpm, beats per minute; mmHg, millimeters of mercury.

9.3.4. Endometrial Biopsy

Primary diagnosis of endometrial biopsy assessment will be summarized at Baseline and at scheduled assessment by treatment group. All endometrial biopsy data will also be provided in a by-patient listing.

Primary diagnosis from pathologist evaluation will be categorized by medical monitor's review in Table 15 and will be summarized using frequencies and percentages, summarized for each treatment group. All endometrial biopsy data will also be provided in by-patient listings.

Table 15: Categories of Primary Diagnosis in Endometrial Biopsies

Normal-Proliferative	• Weakly proliferative • Proliferative • Disordered proliferative
Normal-Secretory/Menstrual/Mixed	• Secretory • Menstrual • Progestational/Decidulized/Mixed
Normal-Atrophic or Minimally Stimulated	• Atrophic • Indeterminate/Inactive
Hyperplasia	• Simple hyperplasia without atypia • Simple hyperplasia with atypia • Complex hyperplasia without atypia • Complex hyperplasia with atypia
Carcinoma	—
Inadequate	—
Missing	—
Additional Diagnosis (Other reported finding)	• Reactive/Inflammatory • Polyp • Metaplasia • Glandular and/or Stromal Breakdown

9.3.5. Bone Mineral Density

Corrected BMD data will be used for analysis as determined by the central radiology laboratory in the 3 prespecified anatomical locations: lumbar spine (L1–L4), total hip, and femoral neck.

BMD at Baseline, Week 12 and Week 24 visits will be summarized descriptively by treatment group and each anatomical location. Percentage changes from Baseline along with 95% CIs of mean percentage changes will be also summarized by treatment group and anatomical location. Mean percentage change from Baseline with its corresponding 95% CI will be plotted by visit, treatment group, and anatomical location.

To support the inclusion of E2/NETA in the treatment regimen, the safety endpoint of mean percent change from Baseline in BMD at the lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal

comparison of the relugolix + E2/NETA group (Group A) versus the relugolix + delayed E2/NETA group (Group B) (details in the Integrated Summary of Safety Statistical Analysis Plan).

In addition, the difference of percentage change from Baseline between treatment groups (relugolix + E2/NETA group versus the relugolix + delayed E2/NETA group at 12 weeks, relugolix + E2/NETA versus placebo group at 12 and 24 weeks, and relugolix + delayed E2/NETA group versus placebo group at 12 weeks) will be summarized at each visit by anatomical location along with the corresponding 95% CIs.

To account for participants whose BMD assessment may have been obtained outside of the protocol-specified window (Week 12 ± 3 weeks, Week 24 ± 3 and 4 weeks), a sensitivity analysis by visit will be conducted that includes all women who underwent DXA at both time points, regardless of whether the image was procured during the prespecified time window.

A mixed-effects model with repeated measures will be used to describe treatment effect on BMD at 12 and 24 weeks. The model will have treatment group, age at Baseline, visit, Baseline BMD value, stratification factors (geographic region and menstrual blood loss volume), race (African American versus Other), and BMI at Baseline as fixed effects using an unstructured variance-covariance matrix. Least square means on each anatomical location will be presented and plotted at each visit with associated 95% CIs. Categorical representation of percentage change from Baseline to 12 and 24 weeks of treatment will be presented by the number and proportion of patients who had BMD declines of ≤ 2%, >2% to 3%, > 3% to 5%, > 5% to 8%, and > 8% by treatment group and anatomical location. The 95% CIs will be provided for the respective proportions.

Categorical changes from Baseline in overall BMD (defined as lumbar spine and total hip) also will be assessed at 12 and 24 weeks. Femoral neck evaluates a smaller area of bone mass than the total hip and is prone to lower precision in the measurement (ISCD Official Positions, 2015; Leslie, 2007). Since femoral neck BMD may be associated with discordant readings compared with the total hip or lumbar spine due to technical considerations, it will not add meaningful interpretation of overall BMD changes in response to treatment.

Z-scores will be summarized by treatment group, visit, and anatomical location with descriptive statistics including 95% CIs, and the number and percentage of patients with a Z-score < -2.0 will be presented by treatment group, visit, and anatomical location.

BMD percentage changes from Baseline will also be summarized by intrinsic factors (eg, age, race, body mass index) and extrinsic factors (eg, geographic region).

9.3.6. Bleeding Pattern

Bleeding patterns will be summarized at Week 24/EOT by treatment group. Three bleeding patterns will be considered: amenorrhea (see Section 7.4.3), cyclic bleeding, and irregular bleeding. Patients with the cyclic bleeding pattern are those who do not meet the definition of amenorrhea and do meet the following conditions:

- 3 to ≤ 12 days of menstruation duration per eDiary at Week 24/EOT window (see Section 7.3.3)

- No more than 2 days of gap of no bleeding (per eDiary) within the menstruation duration.

Patients with the irregular bleeding pattern are those who do not meet the definitions of cyclic bleeding or amenorrhea. The number (and percent) of patients and mean number of bleeding days will be provided by treatment group for each bleeding pattern.

For patients with cyclic or irregular bleeding pattern, the number (and percent) of patients with observed MBL volume falling into the following bleeding intensity groups will be provided:

- **Spotting/negligible bleeding:** MBL volume < 5 mL
- **Light:** MBL volume 10 - 50 mL
- **Moderate:** MBL volume >50 to ≤80 mL
- **Heavy:** MBL volume > 80 mL

For each bleeding intensity category, the mean number of bleeding days will be summarized.

10. REFERENCES

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APPENDICES

APPENDIX 1. SUMMARY OF SECONDARY ENDPOINT ANALYSES

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
Key Secondary Efficacy Endpoints with Alpha Protection					
Proportion of women who achieve amenorrhea over the last 35 days of treatment	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Week 24	Frequency and percentages
% change from Baseline to Week 24 in MBL volume	mITT	Mixed-effects model	P < 0.05	Week 24	LS means for % change
Proportion of women with a hemoglobin ≤10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24	Subset of mITT	Cochran-Mantel-Haenszel test	P < 0.05	Week 24	Frequency and percentages
Change from Baseline to Week 24 in the UFS-QoL Bleeding and Pelvic Discomfort Scale score, a sub-scale of the UFS-QoL Symptom Severity Scale	mITT	Mixed-effects model	P < 0.05	Week 24	LS means for change
Proportion of patients with a maximum NRS score ≤ 1 during the 35 days before the last dose of study drug in the subset of women with a maximum NRS score ≥4 for pain associated with uterine fibroids during the 35 days prior to randomization	Subset of mITT	Cochran-Mantel-Haenszel test	P < 0.05	Week 24/EOT	Frequency and percentages
% change from Baseline to Week 24 in uterine fibroid volume	mITT	ANCOVA model	P < 0.05	Week 24	LS means for % change
% change from Baseline to Week 24 in uterine volume	mITT	ANCOVA model	P < 0.05	Week 24	LS means for % change
Other Secondary Efficacy Endpoints					
Time to achieve MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume as measured by the alkaline hematin method	mITT	Log-rank test/KM method	P < 0.05	Monthly	KM estimates at Week 12 and 24, KM plots, median time to response
Time to achieve amenorrhea	mITT	Log-rank test/KM method	P < 0.05	Monthly	KM plots, median time to response

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
Time to sustained amenorrhea	mITT	Log-rank test/KM method	P < 0.05	Monthly	KM plots, median time to response
Proportion of women in the relugolix Group A versus the placebo Group C who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume at Week 4, Week 12, Week 16, and Week 20	mITT	No comparison		*at Week 4, Week 12, Week 16, and Week 20*	Descriptive
Sustained amenorrhea rate by visit	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Change (absolute and %) from Baseline to Week 24 in hemoglobin for women with a hemoglobin ≤ 10.5g/dL at Baseline	mITT	Mixed-effects model	P < 0.05	Monthly	LS means for % change
Proportion of women who achieve a maximum Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization	Subset of mITT	Cochran-Mantel-Haenszel test	P < 0.05,	Week 12, 24	Frequency and percentages
Mean maximum NRS scores over time	Subset of mITT	Descriptive		Monthly	Means
Proportion of responders who had meaningful reduction of >20 points from Baseline to Week 24 in UFS-QOL Bleeding and Pelvic Discomfort Scale (Q1, Q2 and Q5)	mITT	Cochran-Mantel-Haenszel test	P < 0.05,	Week 12, 24	Frequency and percentages
Proportion of responders who had meaningful increase of > 20 points from Baseline to Week 24 in UFS-QOL revised activities	mITT	Cochran-Mantel-Haenszel test	P < 0.05,	Week 12, 24	Frequency and percentages

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL revised activities domain	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Q11	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Q20	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Q29	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the UFS-QoL Symptom Severity Scale score	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the UFS-HRQL total score	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change in PGA for uterine fibroid related function from Baseline to Week 24	mITT	Mixed-effects model	P <0.05	Monthly	LS means for absolute and change
Change in PGA for uterine fibroid symptoms from Baseline to Week 24	mITT	Mixed-effects model	P < 0.05	Monthly	LS means for absolute and change
Proportion of patients achieving improvement in PGA for uterine fibroid symptoms from Baseline to Week 24	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Proportion of patients achieving improvement in PGA for uterine fibroid related function from Baseline to Week 24	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Safety Related Endpoints					
% Change from Baseline to Week 12 in BMD (pooled data)	Safety population	Mixed-effects model Relugolix Group A vs B	P < 0.05,	Week 12	LS means Diff (95%CI)

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
% Change from Baseline in BMD	Safety population	Mixed-effects model Relugolix Group A vs Placebo at 12/24 weeks; Relugolix Group B vs Placebo at 12 weeks		Week 12, 24	LS means Diff (95%CI)
Exploratory Secondary Efficacy Endpoints					
Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities	mITT	Descriptive		Monthly	Frequency and percentages
Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities	mITT	Descriptive		Monthly	Frequency and percentages

Abbreviations: KM, Kaplan-Meier; LS, least squares; mITT, modified intent-to-treat; NRS, Numerical Rating Scale; Q, question; UFS-HRQL, Uterine Fibroid Scale – Health-related Quality of Life.
[a] P-values are two-sided.

APPENDIX 2. DERIVATION AND PSYCHOMETRIC EVALUATION OF A UFS-QOL BLEEDING AND PELVIC DISCOMFORT SCALE

The BPD Scale was derived from the Symptom Severity Scale of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL). The BPD Scale consists of three items proximal to uterine fibroids that are experienced by most patients, (ie, heavy bleeding during the menstrual period [Question 1], passing blood clots during the menstrual period [Question 2], and feeling tightness or pressure in the pelvic area [Question 5]).

The aim of this appendix is to describe the derivation and psychometric testing process of the BPD Scale. Results of the analyses in this appendix are summarized in Appendix 3 and will be included in the Patient-Reported Outcomes dossier to be submitted at the time of filing for the uterine fibroids registration program.

Exploratory factor analysis and subsequent confirmatory factor analysis were conducted to assess and confirm the factor structure of the Symptom Severity Scale of the UFS-QoL, using data from a phase 2 study of relugolix in uterine fibroids (TAK-385/CCT-001), as well as pooled, blinded data from one-third of patients in the phase 3 studies (MVT-601-3001 and MVT-601-3002). Respective analyses are described in Section 2.1. Based on the results, the factor(s) reflecting symptoms proximal to uterine fibroids and experienced by most patients with uterine fibroids were selected for further psychometric testing.

The psychometric properties of the new scale were assessed using the same pooled, blinded data from the two phase 3 studies of relugolix in uterine fibroids (MVT-601-3001 and MVT-601-3002). These analyses are described in Section 2.2. The blinded data consists of the first third of patients (approximately n = 260) enrolled into the two pivotal studies who have completed the patient global assessment (PGA) for symptoms and the UFS-QoL at Baseline and at Week 24. Of note, for the analyses specified in Section 2.2, only data at Baseline and Week 12 were used; the Week 24 data was used in the responder analyses described in Appendix 3.

2.1. Development of the Bleeding and Pelvic Discomfort Scale Using Phase 2 and Phase 3 Data

From a review of the eight items in the Symptom Severity Scale of the UFS-QoL, it was apparent that the scale consists of different constructs/dimensions. Therefore, the factor structure of the Symptom Severity Scale was assessed, initially using data from the phase 2 study TAK-385/CCT-001 (n = 216).

Of note, in the TAK-385/CCT-001 phase 2 study, the UFS-QoL with a one-month recall period was applied, whereas the UFS-QoL with a three-month recall period is used in the phase 3 studies (MVT-601-3001 and MVT-601-3002). Therefore, confirmatory factor analysis and final psychometric testing of the chosen factor was conducted using blinded phase 3 data (see Section 2.2).

Exploratory Factor Analysis

The exploratory factor analysis was done on phase 2 data to identify the underlying constructs by the most parsimonious factor structure of the eight items in the Symptom Severity Scale. Identification of the number of factors was based on the following criteria:

- Items with primary factor loading > 0.4;
- Factors with large eigenvalues considered as common factors using Kaiser criterion (Kaiser, 1960).

A scree plot was used as a supplemental tool to decide on the number of factors in the final model.

Confirmatory Factor Analysis

Once the number of factors was identified, a confirmatory factor analysis was conducted using blinded, pooled phase 3 data to confirm the factor structure. Only patients who completed the Baseline and Week 24 PGA for symptoms and UFS-QoL assessments were included in this analysis. Model fit was assessed based on the following:

- The goodness of fit as measured by χ^2 and Goodness of Fit Index; a Goodness of Fit Index > 0.9 is considered acceptable;
- The Comparative Fit Index was used to determine the acceptability of the model fit of the discrepancy function adjusted sample size; a Comparative Fit Index > 0.9 (Hu, 1995) was considered an acceptable fit;
- The root mean square error of approximation was used to determine the acceptability of model fit of the square root of the discrepancy between the sample covariance matrix and the model covariance matrix; the root mean square error of approximation had to be < 0.06 (Browne, 1993) to be considered an acceptable fit;
- P-value > 0.05.

Once the final factor structure was identified, the factor reflecting items proximal to uterine fibroids and experienced by almost all patients with uterine fibroids were selected for further evaluation. Of note, this was the BPD Scale.

2.2. Psychometric Analyses Based on Phase 3 Data

The same pooled, blinded data from the first third of patients enrolled in either of the two phase 3 studies (MVT-601-3001 or MVT-601-3002) was used for the psychometric analyses of the BPD Scale. The objective was to psychometrically evaluate the new scale in terms of item performance, reliability, validity, and ability to detect change. Of note, for the analyses specified in this section, only data at Baseline and Week 12 were used. The following analyses were performed:

Item Level Analysis Assessing Ceiling and Floor Effects:

- A descriptive summary of the eight items in the UFS-QoL Symptom Severity Scale at Baseline was provided to examine item distributions and ceiling/floor effects. Low ceiling effects (< 20%) and higher floor effects (> 20%) were expected at Baseline

due to symptom severity of patients with uterine fibroids enrolled in the phase 3 studies.

Internal Consistency:

Internal consistency reliability was assessed for the BPD Scale at Baseline and Week 12 by calculating Cronbach's alpha. Generally, a Cronbach's alpha coefficient (α) ≥ 0.7 indicates an acceptable level of internal consistency.

Item Performance:

- Intercorrelation of items that contribute to the BPD Scale by means of item-total correlation was determined.
- Item discrimination index was assessed for each item based on 1) the BPD Scale scores at single time points, and 2) the change from Baseline to Week 12 in the BPD Scale score to determine the degree to which individual items were able to discriminate between less and more severe patients (Cappelleri, 2014).

Known-Groups Validity:

- Known-groups validity was assessed based on groups defined by Baseline PGA for symptoms severity (five levels). Descriptive statistics of the BPD Scale will be provided for each severity level.

Ability to Detect Change:

Evidence that the new scale can identify differences in scores over time in individuals or groups who have changed with respect to the measurement concept will be investigated by providing the following descriptive statistics:

- Within person change from Baseline to Week 12 in each item on the BPD Scale
- Standardized effect size statistic (SES) for change from Baseline to Week 12 in each item scale. The ability to detect change will be judged based on Cohen's recommendations: small change (SES = 0.20), moderate change (SES = 0.50), and large change (SES = 0.80).

2.3. References

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APPENDIX 3. DERIVATION AND VALIDATION OF THE UFS-QOL BLEEDING AND PELVIC DISCOMFORT SCALE

Results described in this appendix are based on the analyses described in Appendix 2.

3.1. Development of the Bleeding and Pelvic Discomfort Scale Using Exploratory and Confirmatory Factor Analysis

Exploratory factor analysis was conducted on data from the phase 2 study TAK-385/CCT-001 study (n = 216) and the arising factor structure was assessed in a confirmatory factor analysis using data from the phase 3 studies MVT-601-3001 and MVT-601-3002.

3.1.1. Exploratory Factor Analysis Using Phase 2 Data

Exploratory factor analysis results revealed a two-factor solution based on the Kaiser criterion (eigenvalues > 1) and factor loading > 0.40 criteria specified in the analysis plan (see Appendix 2). Factor 1 and Factor 2 had eigenvalues of 3.394 and 1.196, respectively (Table 3.1-1). Three items were found to load adequately onto Factor 1 with loadings greater than 0.40: Item 1 (Heavy Bleeding during Your Period), Item 2 (Passing Blood Clots during Your Period), and Item 5 (Feeling Tightness or Pressure in Pelvis; see Table 3.1-2). Two items loaded onto Factor 2 with loadings larger than the prespecified level: Item 6 (Frequent Urination in Daytime) and Item 7 (Frequent Nighttime Urination). Item 8 (Feeling Fatigued) showed a loading value on Factor 1 just below the prespecified threshold (0.399) and showed evidence of cross-loading with the Factor 2 (0.288). An additional factor with a moderate eigenvalue (0.62) was considered based the scree plot (Figure 3.1-1) and factor loadings of its associated items (Item 3: Fluctuation in Duration of Menstruation, 0.416; Item 4: Fluctuation in Length of Monthly Cycle, 0.995; Table 3.1-2).

Overall the results show support for a seven-item three-factor model. Due to multi-factor loading, Item 8 (Feeling Fatigued) remains a single-item symptom and is not scored as part of any factor.

Figure 3.1-1: Scree Plot and Variance Explained for UFS-QoL Symptom Severity Scale Factors in TAK-385/CCT-001

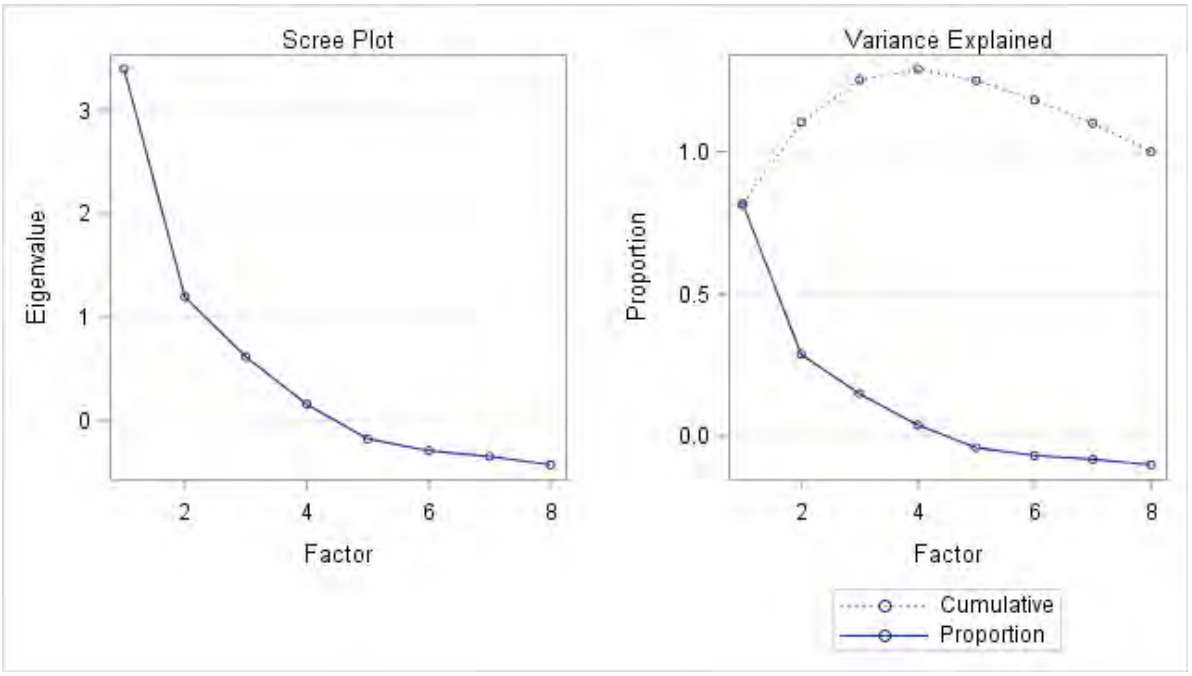


Table 3.1-1: Exploratory Factor Analysis for the UFS-QoL Symptom Severity Scale in TAK-385/CCT-001

Item	Eigenvalue	Difference	Proportion	Cumulative
1	3.394	2.198	0.816	0.816
2	1.196	0.576	0.288	1.104
3	0.620	0.458	0.149	1.253
4	0.162	0.332	0.039	1.292
5	-0.170	0.114	-0.041	1.251
6	-0.284	0.057	-0.068	1.183
7	-0.341	0.079	-0.082	1.101
8	-0.419	—	-0.101	1.000

Table 3.1-2: Factor Loadings for the UFS-QoL Symptom Severity Scale in TAK-385/CCT-001

Items		Factor1	Factor2	Factor3
Q2	Passing blood clots during your period	**0.763**	0.105	0.073
Q1	Heavy bleeding during your period	**0.759**	0.091	0.123
Q5	Feeling tightness or pressure in pelvis	**0.467**	0.175	0.167
Q8	Feeling fatigued	0.399	0.288	0.078
Q6	Frequent urination in daytime	0.114	**0.965**	0.069
Q7	Frequent nighttime urination	0.212	**0.630**	0.013
Q4	Fluctuation in length of monthly cycle	0.039	0.092	**0.995**
Q3	Fluctuation in duration of menstruation	0.178	0.003	**0.416**

Extraction method: maximum likelihood. Rotation method: orthogonal.

3.2. Development of the Bleeding and Pelvic Discomfort Scale Using Confirmatory Factor Analysis Based on Phase 3 Data

The exploratory factor structure arising from the phase 2 data was assessed using data from the phase 3 studies MVT-601-3001 and MVT-601-3002.

Analyses were based on pooled, blinded data from the first one third of patients enrolled in the two phase 3 studies of relugolix in uterine fibroids (MVT-601-3001 and MVT-601-3002), who completed the patient global assessment of symptoms (PGA) and the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) at Baseline and at Week 24.

3.2.1. Confirmatory Factor Analysis using Phase 3 Data

A confirmatory factor analysis was completed using blinded data from one third of phase 3 patients. The acceptance criteria of the confirmatory factor analysis were prespecified as a Goodness of Fit Index > 0.90 and a Comparative Fit Index > 0.90, a root mean square error of approximation < 0.06 and a non-significant p-value to show that the null-hypothesis that the data fits the three-factor model was not rejected (Table 3.2-1).

Factor loadings for the seven-item three-factor model supported the three-factor solution proposed by the exploratory factor analysis in the above described analyses using phase 2 data. Results indicated that the three-factor model, excluding item 8, had a Goodness of Fit Index and a Comparative Fit Index of 1.00 and a root mean square error of approximation of 0.00 (90% CI = 0.00-0.02). The test of model fit returned a p-value of 0.9394. The null hypothesis that the data fit the model was not rejected (see Table 3.2-1). Under this model, Item 5 (Feeling Tightness or Pressure in Pelvis) also cross-loaded onto Factor 2, assessing urinary symptoms.

Table 3.2-1: Confirmatory Factor Analysis of the UFS-QoL Symptom Severity Scale without Item 8: Model Fit Statistics at Baseline (MVT-601-3001 and -3002)

Model Fit Statistics[a]					
Model		**CFI**	**RMSEA (90%CI)**	**GFI**	**P-value**
3-Factor Model (7-item)		1.000	0.000 (0.00-0.02)	1.000	0.9394
Factor Loading[b]					
			Factor1	**Factor2**	**Factor3**
Q1	Heavy bleeding during your period		**0.7314**	0.2672	0.2024
Q2	Passing blood clots during your period		**0.7620**	0.1503	0.2099
Q3	Fluctuation in duration of menstruation		0.3263	0.1861	**0.6909**
Q4	Fluctuation in length of monthly cycle		0.1689	0.1561	**1.0323**
Q5	Feeling tightness or pressure in pelvis		**0.4644**	**0.4657**	0.1965
Q6	Frequent urination in daytime		0.2503	**0.7727**	0.1300
Q7	Frequent night time urination		0.1553	**0.8605**	0.1538

Abbreviations: CFI, comparative fit index; CI, confidence interval; GFI, goodness of fit index; RMSEA, root mean square error approximation.
[a] Model fit statistics allow for assessment of the model appropriateness.
[b] Rotation Method: Orthogonal.

In order to further assess the performance of the Fatigue item, which was excluded following the exploratory factor analysis due to cross-loading, the confirmatory factor analysis was reconducted with the inclusion of this item in Factor 1. Results showed that the eight-item three-factor model had a Goodness of Fit Index of 0.996, a Comparative Fit Index of 1.00 and a root mean square error of approximation of 0.00 (90% CI = 0.00-0.05). The test of model fit returned a p-value of 0.8056. However, the results for Item 8 showed a cross-loading of this item at 0.417 on Factor 1 and 0.437 on Factor 2 (Table 3.2-2). This continued cross-loading supports the exclusion of this item in the scoring of any factor (Table 3.2-2).

Table 3.2-2: Confirmatory Factor Analysis of the UFS-QoL Symptom Severity Scale with Item 8 included: Model Fit Statistics at Baseline (MVT-601-3001 and 3002)

Model Fit Statistics[a]					
Model		**CFI**	**RMSEA (90%CI)**	**GFI**	**P-value**
3-Factor Model (8-item)		1.000	0.000 (0.00-0.05)	0.996	0.8056
Factor Loading[b]					
			Factor1	Factor2	Factor3
Q1	Heavy bleeding during your period		**0.732**	0.265	0.211
Q2	Passing blood clots during your period		**0.750**	0.150	0.226
Q3	Fluctuation in duration of menstruation		0.296	0.175	**0.767**
Q4	Fluctuation in length of monthly cycle		0.180	0.167	**0.932**
Q5	Feeling tightness or pressure in pelvis		**0.473**	**0.465**	0.206
Q6	Frequent urination in daytime		0.251	**0.757**	0.137
Q7	Frequent night time urination		0.150	**0.876**	0.156
Q8	Feeling fatigued		**0.417**	**0.437**	0.136

Abbreviations: CFI, comparative fit index; CI, confidence interval; GFI, goodness of fit index; Q, question; RMSEA, root mean square error of approximation.
[a] Model fit statistics allow for assessment of the model appropriateness.
[b] Rotation Method: Orthogonal.

3.3. Classical Test Theory Psychometric Analyses of the Bleeding and Pelvic Discomfort Scale Based on Phase 3 Data

Each of the above-described factor analyses showed that a seven-item three-factor solution was appropriate for the UFS-QoL Symptom Severity Scale. Following this confirmation, blinded psychometric appraisal of the measure was implemented to further understand the performance of the items and subscales of the UFS-QoL Symptom Severity Scale. For the item level analysis, all items were assessed. For subscale level analysis, the analysis was focused, primarily, on the evaluation of the Factor 1 – the Bleeding and Pelvic Discomfort (BPD) Scale. The BPD Scale was selected as the primary focus for further psychometric evaluation, as it presents clinical and patient-reported symptoms proximal to the disease and is associated with high symptom burden experienced by most patients.

Analyses were based on pooled, blinded data from the first one third of patients enrolled in the two phase 3 studies of relugolix in UF (MVT-601-3001 and MVT-601-3002) who completed the PGA for symptoms and the UFS-QoL at Baseline and at Week 24. Of note, for the analyses specified in this section, only data at Baseline and Week 12 were used.

3.3.1. Item Level Analysis of the UFS-QoL Symptom Severity Scale

UFS-QoL Symptom Severity Scale item responses were assessed for floor (highest possible severity) and ceiling effects (lowest possible severity). Overall, the measure showed no ceiling effects (response option 1, Table 3.3-1, demonstrating that the items have scope to capture

patient improvement in disease burden. A greater proportion of patients responded at floor level (response option 5; range =11.15 to 36.15%), which is expected at the start of a clinical trial. All response options for all items were used, showing a good coverage of the range of disease burden. When considering BPD Scale items, all items showed a range of responses that covered the response scale, with over 50% of patients reporting being a (very) great deal distressed by heavy bleeding during menstrual period (Item 1), passing blot clots during menstrual period (Item 2), and feeling of tightness or pressure in the pelvic area (Item 5).

Table 3.3-1: Summary of UFS-QoL Symptom Severity Scale Response at Baseline by Items in MVT-601-3001 and 3002

	Q1 (N = 260)		Q2 (N = 260)		Q3 (N = 260)		Q4 (N = 260)		Q5 (N = 260)		Q6 (N = 260)		Q7 (N = 260)		Q8 (N = 260)	
Response	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1	4	(1.54%)	4	(1.54%)	44	(16.92%)	63	(24.23%)	21	(8.08%)	48	(18.46%)	54	(20.77%)	13	(5.00%)
2	15	(5.77%)	30	(11.54%)	48	(18.46%)	37	(14.23%)	24	(9.23%)	35	(13.46%)	53	(20.38%)	21	(8.08%)
3	53	(20.38%)	61	(23.46%)	66	(25.38%)	69	(26.54%)	57	(21.92%)	77	(29.62%)	64	(24.62%)	59	(22.69%)
4	101	(38.85%)	71	(27.31%)	64	(24.62%)	62	(23.85%)	96	(36.92%)	62	(23.85%)	55	(21.15%)	82	(31.54%)
5	87	(33.46%)	94	(36.15%)	38	(14.62%)	29	(11.15%)	62	(23.85%)	38	(14.62%)	34	(13.08%)	85	(32.69%)

Abbreviations: N, number of patients; n, number of patients in subset; Q, question.

3.3.2. Scale Level Analysis of the BPD Scale

3.3.2.1. Internal Consistency

Internal consistency was assessed for the BPD Scale at Baseline and Week 12. Reliability was acceptable at Baseline (> 0.70) and good at Week 12 (> 0.80; Table 3.3-2).

Table 3.3-2: Cronbach's Alpha Coefficient of BPD Scale by VISIT (MVT-601-3001 and 3002)

		Q1	Q2	Q3	
	n	Mean (SD)	Mean (SD)	Mean (SD)	**Alpha[a]**
Baseline	260	3.97 (0.95)	3.85 (1.09)	3.59 (1.18)	0.768
Week 12	258	2.75 (1.47)	2.69 (1.46)	2.64 (1.36)	0.882

Abbreviations: n, number of patients; Q, question; SD, standard deviation.
[a] Cronbach Coefficient Alpha

3.3.2.2. Item-to-Total Correlations

Item-to-total correlations were assessed to ensure that each item was associated with the BPD Scale score. Correlations demonstrate that each of the items have a strong relationship with the total score at Baseline and at Week 12 ($r > 0.50$) (Table 3.3-3). Correlations improved at Week 12, which represents a greater spread of the data across each item's five-point response scale, further supporting the relationship of these items to the BPD total score.

Table 3.3-3: Intercorrelation of Items in BPD Scale by Visit (MVT-601-3001 and 3002)

Question	**Baseline** **N = 260**	**Week 12** N = 258
Q1	0.670	0.802
Q2	0.620	0.845
Q5	0.533	0.674

Note: Intercorrelation calculated using Pearson's correlations.

3.3.2.3. Item Discrimination Indices

An item discrimination index was employed to assess the ability of each item to discriminate between high and low severity patients. At Baseline, the discrimination index represents each item's ability to differentiate patients on the BPD Scale scores at a single time point, and at Week 12, the discrimination index represents the ability to differentiate patients based on their level of change from Baseline to Week 12 in the BPD Scale score.

Results show that all items had a discrimination index above 0.60, demonstrating that BPD Scale items are able to discriminate between high- and low-severity patients both when assessing single time point scores and change over time (Table 3.3-4).

Table 3.3-4: Item Discrimination Index of BPD Scale (MVT-601-3001 and 3002)

	Q1	Q2	Q5
Baseline (n = 260)	0.815	0.954	0.923
Week 12 (n = 258)	0.915	0.986	0.836

Abbreviations: n, number of patients; Q, question.
Note: BPD scale upper/lower ranges**:** Upper = at least 65-point reduction, Lower = at most 10-point reduction.

3.3.2.4. Known-Groups Validity

A known-groups analysis assessed the descriptive BPD score and score ranges for patients stratified by level of severity reported on the PGA (symptoms). Results from the known-groups validity assessment show that mean and median BPD Scale scores increase monotonically in line with PGA symptom severity (Table 3.3-5).

3.3.2.5. Ability to Detect Change

The BPD Scale's ability to detect change was assessed though the difference in BPD Scale scores over time in patients who have changed with respect to the measurement concept as measured by the PGA (symptoms). For each PGA stratified group, within person change from Baseline to Week 12 and standardized effect size statistics (SES) for change over the same period were assessed. SES statistics judged were based on Cohen's recommendations (small change, 0.20; moderate change, 0.50; large change, 0.80).

Results showed that the mean change for improving PGA categories had a monotonically increasing pattern from patients who had a PGA change of 0 to patients who had a PGA improvement of -4 (Table 3.3-6). Worsening groups (PGA change of +1 or +2) had very low levels of mean change, with wide standard deviations around the mean due to the low sample size in these categories.

In line with expectations, the SES statistics for the improvement categories (PGA score change of -1 to -4) were large (> 0.80) compared to the moderate SES found in the patients who reported no change (PGA score change of 0; SES = 0.55).

Table 3.3-5: Summary Statistics of BPD Scale Score at Baseline by PGA (symptoms) Response (MVT-601-3001 and 3002)

	Baseline BPD Scale Score[a]						
Baseline PGA	**N**	**Mean**	**SD**	**Median**	**Q1, Q3**	**Min**	**Max**
1	7	53.57	28.81	58.33	25.00, 75.00	16.67	91.67
2	21	59.92	26.56	58.33	41.67, 75.00	8.33	100.00
3	96	62.33	21.18	66.67	41.67, 75.00	8.33	100.00
4	89	75.09	19.48	75.00	66.67, 91.67	16.67	100.00
5	47	83.51	16.53	91.67	75.00, 100.00	41.67	100.00

Abbreviations: BPD, bleeding and pelvic discomfort; max, maximum; min, minimum; N, number of patients; PGA, Patient Global Assessment; Q1, first quartile; Q3, third quartile; SD, standard deviation.
a Transformed Score.

Table 3.3-6: Summary Statistics of Change from Baseline BPD Scale Score to Week 12 by PGA (symptoms) Change from Baseline (MVT-601-3001 and 3002)

PGA Change Category[a]	N	Mean	SD	95% CI	Median	Q1, Q3	Min	Max	Effect Size[b]
-4	23	-48.19	(42.27)	(-66.47, -29.91)	-66.67	-83.33, 0.00	-100.00	25.00	-2.93
-3	50	-49.33	(33.16)	(-58.76, -39.91)	-54.17	-75.00, -25.00	-100.00	33.33	-2.41
-2	74	-27.70	(30.75)	(-34.83, -20.58)	-25.00	-41.67, 0.00	-91.67	25.00	-1.25
-1	48	-23.09	(28.57)	(-31.39, -14.79)	-16.67	-33.33, -8.33	-100.00	33.33	-1.01
0	39	-10.68	(20.32)	(-17.27, -4.10)	-8.33	-25.00, 0.00	-66.67	33.33	-0.55
1	14	1.79	(19.11)	(-9.25, 12.82)	-4.17	-16.67, 8.33	-16.67	33.33	0.07
2	6	-1.39	(29.54)	(-32.39, 29.61)	-12.50	-25.00, 16.67	-25.00	50.00	-0.05

Abbreviations: BPD, blood and pelvic discomfort; CI, confidence interval; max, maximum; min, minimum; N, number of patients; PGA, Patient Global Assessment; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Note: Statistics calculated using transformed score of BPD scale.
[a] The PGA is a five-point, single item patient-reported outcomes tool that measures patient's symptoms. The PGA change category with -4 = Marked Improvement; 0 = No Change, +4 = Markedly Worse.
[b] Standardized effect sizes are calculated as the mean divided by the standard deviation.

3.4. Conclusions

The exploratory factor analysis offered support for a three-factor solution, which included factors assessing Bleeding and Pelvic Discomfort, Urinary Symptoms, and Fluctuation in Menstruation. The Fluctuations in Menstruation factor had an eigenvalue < 1 but had items that loaded at greater than 0.40 and made theoretical sense as a construct.

The exploratory factor analysis showed that Item 8, measuring fatigue, cross-loaded on two factors (Bleeding and Pelvic Discomfort and Urinary Symptoms). Since fatigue is a multidimensional concept that can assess impacts and/or symptoms concurrently, it was not included in the final factor structure. Confirmatory factor analysis on the seven-item three-factor solution provided support for the exploratory factor structure; however, Item 5 cross-loaded between the BPD and Urinary Symptoms factors in this analysis. As Item 5 (Feeling Tightness or Pressure in Pelvis) is a proximal symptom of uterine fibroids, this item was retained as part of the BPD factor.

To ensure that fatigue was not being inappropriately excluded from the three-factor structure, an additional confirmatory factor analysis was conducted with fatigue included within the BPD factor. The inclusion of fatigue in this model continued to show the expected cross-loading of this item. This analysis confirmed that the multidimensional concept of fatigue was not suitable for inclusion in the BPD factor.

The BPD factor, which assesses symptomology most proximal to the disease, was further assessed through classical test theory psychometric evaluation. The results showed that the items of the BPD Scale work cohesively to inform the total score of the measure, and adequately distinguish between severities. At a score level, descriptive statistics were able to support the construct validity and responsiveness of the BPD Scale through showing a monotonic improvement in BPD Scale score in line with patient self-reported improvement on the PGA (symptoms). Additionally, by showing that the items of the BPD Scale perform well together, the psychometric results help to further support the inclusion of the cross-loading Item 5 on the BPD Scale.

APPENDIX 4. APPROACH TO ESTIMATING THE RESPONDER THRESHOLD OF THE UFS-QOL BLEEDING AND PELVIC DISCOMFORT SCALE

The Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort (UFS-QoL BPD) Scale includes the following items:

During the previous 3 months, how distressed were you by:

- Heavy bleeding during your menstrual period;
- Passing blood clots during your menstrual period;
- Feeling tightness or pressure in your pelvic area.

Response options include:

- Not at all;
- A little bit;
- Somewhat;
- A great deal;
- A very great deal.

The summary score of the three items included in the UFS-QoL BPD Scale ranges from 0 to 100, where a higher score indicates a higher level of distress and a lower score indicates a lower level of distress.

Change from Baseline to Week 24 in the BPD Scale score is an alpha-protected key secondary endpoint of the pivotal studies (MVT-601-3001 and MVT-601-3002) to evaluate the treatment benefit of relugolix + E2/NETA (Group A) compared with placebo (Group C). Additionally, a responder analysis will be performed between the two groups with respect to proportion of patients who have achieved a meaningful reduction from Baseline to Week 24 in BPD Scale score. This appendix describes the approach used to derive the responder threshold, including both the quantitative and supportive qualitative methods and the respective results.

The meaningful change threshold is the smallest reduction in the BPD Scale score that is considered meaningful by patients (Cohen, 1988; Crosby, 2003; Revicki, 2008; Cappelleri, 2014; Coon, 2018). The magnitude of a meaningful change threshold depends on the magnitude of the correlation between the BPD Scale change score and the Patient Global Assessment (PGA) of symptom severity (anchor) change and the variability of change on the BPD Scale by improvement categories on the PGA of symptom severity (described in Section 4.2.2). Several anchor-based methods will be used; however, the primary analysis will be a measure of central tendency for each improvement category (see Section 4.2.3). Anchor-based methods will use data collected on:

- The BPD Scale score at Baseline and Week 24; and
- The PGA of symptom severity score at Baseline and Week 24.

Results from the anchor-based analyses will be supported by qualitative data collected in a patient interview study (MVT-601-037), a sub-study of the phase 3 trials, in which patients from

selected sites in the United States (US) provided feedback on what they considered to be a meaningful change on the BPD Scale and the PGA of symptom severity (described in Section 4.2.4).

4.2. Statistical Analyses Plan for Estimation of the Responder Threshold

4.2.1. Anchor and Its Correlation with UFS-QoL Endpoint

The PGA of symptom severity uses a five-point verbal rating scale and asks the patient:

> "How severe were your uterine fibroids symptoms, such as heavy bleeding over the last four weeks?"
>
> Response options include:
>
> - Not severe;
> - Mildly severe;
> - Moderately severe;
> - Very severe;
> - Extremely severe.

The categorical change from Baseline to Week 24 in PGA of symptom severity score will be derived, leading to nine possible outcomes ranging from +4 (denoting worsening) to -4 (denoting improvement). The change in PGA of symptom severity at Week 24 will be used as the anchor (see Table 4.2-1).

4.2.2. Target Anchor Category

The target anchor category is the anchor category that represents the minimum meaningful change and is used as the starting point to identify potential candidates for a meaningful change threshold. For the two pivotal studies, the target anchor category will be a one-point category improvement on the PGA of symptom severity score (see Table 4.2-1), as this is typically considered as a minimal clinical important difference on a five-point Likert scale.

Table 4.2-1: Change in PGA of Symptom Severity as Anchor

Anchor	Anchor Change Category	Potential Target Anchor Change Category (To Be Used for Estimation of Meaningful Change Threshold)
Change in PGA of symptom severity	-4, -3, -2, -1 (improvement), 0 (same), +1, +2, +3, +4 (worsening)	-1-category change (improvement)

Abbreviations: PGA = patient global assessment.

4.2.3. Anchor-Based Methods

To determine the meaningful change threshold for the reduction in USF-QoL BPD Scale score, the anchor-based analyses described below will be performed.

The category (or point) change in PGA of symptom severity score will be used as the anchor to classify patients into response groups depending on their level of symptom severity change from Baseline to Week 24 (see Table 4.2-1). Uncollapsed, categorical change on the PGA will range from +4 to -4. Collapsed, categorical change will be considered based on the distribution of change categories on the PGA of symptom severity. Usually the collapsing occurs on the tails with extreme worsening (+4) or improvement (-4).

Among the anchor-based analyses described below, the within-group analysis will be primary and other analyses (including between-group analysis) are supportive.

4.2.3.1. Correlation with Anchor

Correlation between the categorical change on the PGA of symptom severity score and the change in the BPD Scale score will be evaluated at Week 24, using blinded pooled data from the first third of the enrolled patients from the two pivotal studies who have completed Week 24 visits and have the corresponding PGA of symptom severity data available (denoted as the "threshold determination analysis set"). Polyserial correlation coefficient will be used with a criteria value of > 0.30 indicating meaningful correlation (Crosby, 2003; Revicki, 2008; Cappelleri, 2014; Coon, 2018).

4.2.3.2. Within-Group Meaningful Change

Magnitude of change from Baseline to Week 24 in BPD Scale score will be calculated within each anchor category group. Changes in BPD Scale scores are negative for symptom reductions and positive for symptom increases.

Descriptive statistics (*n*, mean change, median change, 25th and 75th percentiles, standard deviation [SD], confidence interval [CI], and standardized effect size [SES]) will be reported for the changes in BPD Scale scores by anchor category. The SES will be calculated for each level of anchor category group by dividing the mean change score of BPD Scale from Baseline by the Baseline SD of the anchor category group. The impact of treatment will be judged based on Cohen's recommendations (1988): small change (SES = 0.20), moderate change (SES = 0.50), and large change (SES = 0.80). Significance associated with within-patient change will be evaluated using paired t-tests on the change in BPD Scale score separately for each level of improvement on the anchor.

4.2.3.3. Supportive Analysis of Between Group Meaningful Change Using Analysis of Variance

Analysis of variance (ANOVA) will be used to determine whether a difference in mean change scores from Baseline to Week 24 on the UFS-QoL BPD Scale exists between the categorical change groups (or the collapsed groups, as appropriate). Providing there is a significant change in UFS-QoL BPD Scale scores between the (collapsed) anchor groups, the between-group differences will be explored. Any anchor group with at least 15 patients will be included in this analysis. An anchor group with < 15 patients (usually occurring on the tails with extreme

worsening [+4] or improvement [-4]) will be collapsed with its adjacent group as appropriate. Comparison of the anchor groups of interest between the target anchor (-1 change category) and the "0 change" category will be performed using a t-test. The statistically significant difference on the BPD Scale change scores corresponding to a 1-category change on the PGA of symptom severity can be used as supportive information for estimating the meaningful change threshold.

4.2.3.4. Visualizing Cumulative Distribution Function and Probability Distribution Function Plots by Anchor Category Group

Anchor-based meaningful change will also be evaluated using cumulative distribution function (CDF) plots utilizing the Kernel smoothing for all anchor category groups, based on cumulative change in UFS-QoL BPD Scale scores for all available changes from Baseline to Week 24. Specifically, the CDF plot for each anchor category displays the probability (presented on the y-axis) of patients who have achieved a given absolute change of X or less in BPD Scale score from Baseline to Week 24 for each point change along the range of possible absolute changes (from -100 [maximum reduction] to 0 [no change] to 100 [maximum increase]) expressed on the x-axis.

Similarly, the smooth probability density function (PDF) will also be plotted for each anchor category group over the range of absolute changes in BPD Scale scores. These probabilities are plotted on the y-axis, with the BPD Scale change score on the x-axis.

The CDF and PDF curves are delineated by anchor improvement category (from -4 to +4) displaying the center and separation between the curve for the target anchor group and the curve for the group reporting no change on PGA of symptom severity. It is expected that the CDF curves will not cross between the change category groups (eg, monotonic increase from no change to slightly improved and moderately improved).

4.2.4. Determining a Meaningful Change Threshold Using the Totality-of-Evidence Approach

The meaningful change threshold will be determined using the totality of evidence from the results of above quantitative anchor-based analyses; results from the interview study (MVT-601-037) will be used as supportive evidence.

The results of these analyses and proposed thresholds will be included into the Patient-Reported Outcome dossier to be submitted at the time of filing.

4.3. Results from Anchor-Based Analyses

4.3.1. Correlation of Change in BPD with PGA of Symptom Severity

Meaningful change for the UFS-QoL BPD Scale was derived based on anchor-based methods, supported by cumulative distribution function (CDF) and probability density function (PDF) curves. To assess the suitability of the selected anchor, PGA of symptom severity, a polyserial correlation was calculated between change on the PGA from Baseline to Week 24 and the change from Baseline to Week 24 on the BPD Scale. The change in the PGA was moderately correlated (r = 0.57) with the change on the BPD Scale (Table 4.3-1). Given that the PGA is less complex than the BPD scale, this result indicates that the PGA is a suitable anchor for the BPD Scale.

4.3.2. Improvement on BPD Scale by PGA Change Category

Uncollapsed changes on the PGA were used to determine minimal meaningful improvement on the BPD Scale (Table 4.3-1). Improvement on the BPD Scale increased monotonically for all the categories from "no change (0)" to "1-category improvement (-1)" to "2-category improvement (-2)" to "3 category improvement (-3)" with nonoverlapping 95% CIs for mean change of the groups. Table 4.3-1 shows further that a 1-category improvement (-1) is associated with a 27.31-point mean improvement in the BPD Scale score at Week 24 compared with Baseline, with a 95% CI [-35.42, -19.19], a large SES = -1.21, and a median improvement of 25.00 points.

Table 4.3-1: Summary of Change from Baseline to Week 24 in UFS-QoL BPD Scale by PGA for Symptom Severity Change Category (mITT Population)

PGA Change Category	N = 255	Change in BPD					Correlation between PGA Change and BPD Change[a]
		Mean (SD)	Median	95% CI	p-value[b]	SES[c]	
4-Category deterioration (+4)	0						0.57
3-Category deterioration (+3)	2	-12.50 (5.89)	-12.5	-65.44, 40.44	0.2048	-2.12	
2-Category deterioration (+2)	2	0.00 (11.79)	0	-105.89, 105.88	1.00	0.0	
1-Category deterioration (+1)	21	-10.32 (16.22)	-8.33	-17.70, -2.93	0.0086	-0.54	
0-Category deterioration (0)	47	-9.93 (23.09)	-8.33	**-16.71**, -3.15	0.005	-0.42	
1-Category improvement (-1)	47	**-27.31** (27.62)	-25.00	-35.42, **-19.19**	< 0.0001	-1.21	
2-Category improvement (-2)	68	-42.16 (25.71)	-41.67	-48.38, -35.93	< 0.0001	-1.93	
3-Category improvement (-3)	45	-61.85 (26.62)	-66.67	-69.85, -53.85	< 0.0001	-3.25	
4-Category improvement (-4)	23	-54.35 (32.65)	-66.67	-68.47, -40.23	< 0.0001	-4.12	

Abbreviations: BPD = bleeding and pelvic discomfort; CI = confidence interval; mITT = modified intent-to-treat; PGA = patient global assessment; SD = standard deviation; SES = standardized effect size.
mITT is used to calculate change from Baseline score at Week 24 and includes patients from the mITT population who have available change from Baseline data at Week 24.
[a] Polyserial correlation coefficient between change in BPD Scale and change in PGA of symptom severity.
[b] The p-value for each individual change group is derived from a paired (within-sample) t-test assessing the difference over time.
[c] SES is calculated as the mean divided by the SD of Baseline. SES is judged as small = 0.2, moderate = 0.5, and large = 0.8 (Cohen 1988).

Table 4.3-2 highlights that the difference between the "1-category improvement" and the "no change" groups (mean = -17.38 with a 95% CI of [-27.81, -6.94]) was statistically significant (p = 0.0013) and had a moderate SES = -0.736, which also supports the notion that patients interpreted these change categories as distinct.

Patients were able to distinguish between the PGA improvement categories, as demonstrated by the nonoverlapping CIs (in Table 4.3-2) for their UFS-QoL BPD Scale scores and as illustrated

by the clear separation between the CDF curves presented in Figure 4.3-1. Since statistically significant differences existed in patient responses on the BPD Scale between the "1-category improvement (-1)" option and the "no change" and "2-category improvement (-2)" options, a 1-category improvement on the PGA was considered a meaningful target anchor category for assessing the responder threshold on the BPD Scale. Although a 2-category improvement could have been considered for deriving the meaningful change threshold, such a threshold would not qualify as being the *minimum* threshold possible. Given the statistical difference between the 1- and 2-category improvements and the fact that patients were able to distinguish between the two response options (to be taken up shortly), the evidence supports using a 1-category improvement on the PGA for estimating the minimum meaningful change threshold. This decision is also supported by qualitative evidence generated from the Exit Interview study (see Section 4.2.4).

Table 4.3-2: Summary of Change from Baseline to Week 24 in BPD Scale Between Target Anchor (-1) and No Change (0) in PGA of Symptom Severity (mITT Population)

Anchor	Categorical Change	N	Mean Change from BL	SD	95% CI	p-value[a]	Baseline SD	SES
PGA	1-category improvement (-1)	47	-27.31	27.62	-35.42, -19.19		22.63	
	No change (0)	47	-9.93	23.09	-16.71, -3.15		23.61	
	Difference		-17.38	25.46	-27.81, -6.94	0.0013		-0.736[b] -0.790[c]

Abbreviations: ANOVA = analysis of variance; BL = Baseline; BPD = bleeding and pelvic discomfort; CI = confidence interval; mITT = modified intent-to-treat; PGA = patient global assessment; SD = standard deviation; SES = standardized effect size.

[a] The p-value is based on t-test for difference in mean change in BPD score between the 2 anchor groups (-1 and 0) from the ANOVA in which the +2, +3, and +4 groups were collapsed with the +1 group due to 0 or few patients in the respective groups.

[b] SES is calculated as the mean difference divided by the SD of Baseline for no change group. They are judged as small = 0.2, moderate = 0.5, and large = 0.8 (Cohen 1988).

[c] SES calculated as the mean difference divided by the standard deviation of Baseline for pooled from all categories (Glass 1976).

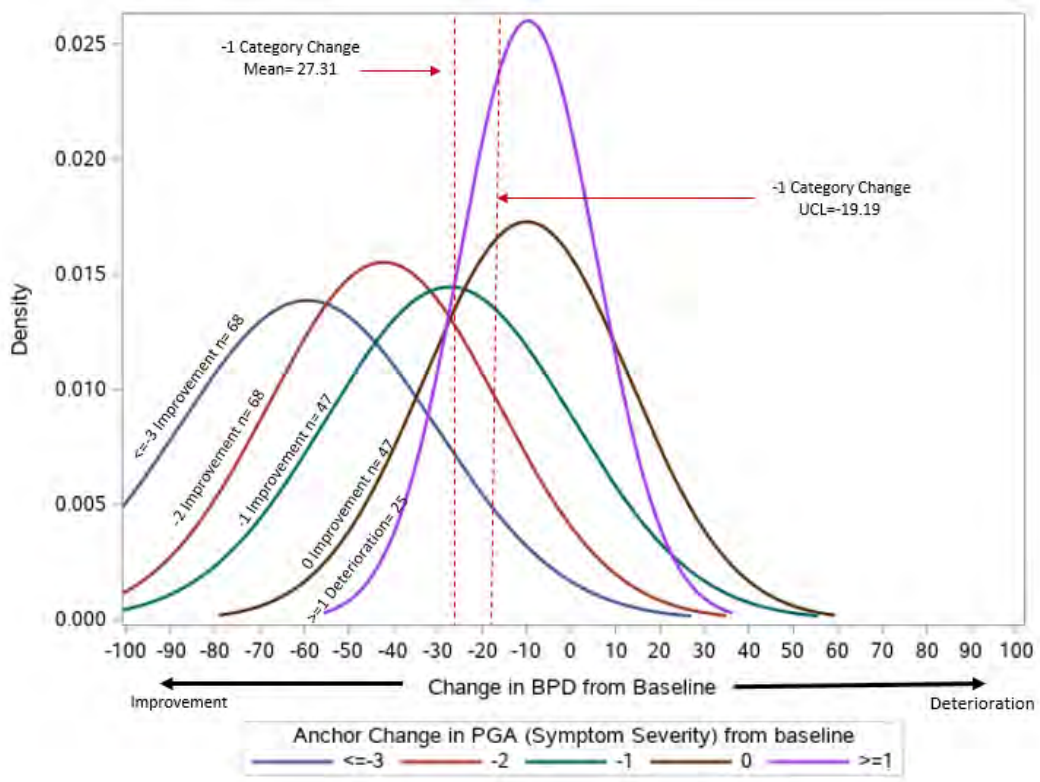
4.3.3. Estimation of Responder Threshold

Examination of the PDF curves, presented in Figure 4.3-1, indicates that the dispersion is roughly the same for the options between "> 3 category improvement" and "no change." The crossing of the "no change" and "1-category improvement" PDF curves at approximately -24 points (ie, a 24-point improvement on the BPD between Baseline and Week 24) indicates the meaningful change threshold is greater (less negative) than this value, because to the left of the value the "1-category improvement" was more probable than the "no change" curve. That is, to the left of this point (larger improvements) patients were more likely to be responders than to the right of this point. However, since the goal is to establish the minimum meaningful change threshold, the value -24 points is likely too conservative.

Using the mean or median values for measuring improvement in the BPD Scale would also yield estimates that are too conservative, because expected values do not necessarily constitute a *minimum* meaningful change threshold for patients. That is, nearly half the patients stratified in

the PGA "1-category improvement" who reported changes smaller than (to the right of) the mean or median on the BPD Scale would be classified as nonresponders by using the mean or median as the threshold despite of their reporting "1-category improvement." A less conservative, though still plausible estimate for the minimal meaningful change threshold is the upper bound of the 95% CI for mean change in the "1-category improvement" group. Its use will result in a smaller proportion of patients being classified as nonresponders in change on the BPD Scale than the expected value (ie, the mean). According to the uncollapsed anchor-based analysis (Table 4.3-1), this value is approximately -19 (ie, a 19-point improvement on the BPD Scale between Baseline and Week 24). Selection of this value is supported by the fact that the mean changes are statistically significantly different (Table 4.3-2) between "no change" and "1-category improvement" groups with clear separation of the respective 95% CIs for mean change. Of note, a value as low as -17 could also be selected, since it is less than the lower-bound 95% CI estimate of -16.71 for the "no change" group.

Figure 4.3-1: PDF of the Change in UFS-QoL BPD Scale by PGA Anchor Change Category (Collapsed)

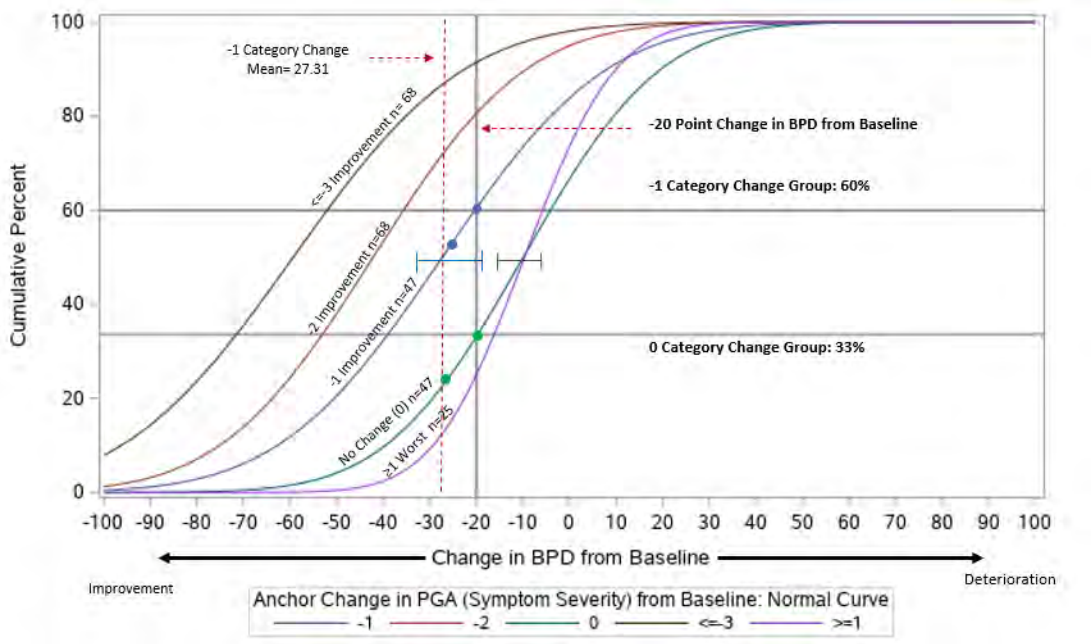


Abbreviations: BPD = bleeding and pelvic discomfort; PGA = patient global assessment; UCL = upper confidence limit.

Examination of the CDF curves for the potential minimum meaningful threshold value of -19 points on the BPD Scale allows one to estimate the cumulative percent of patients that would

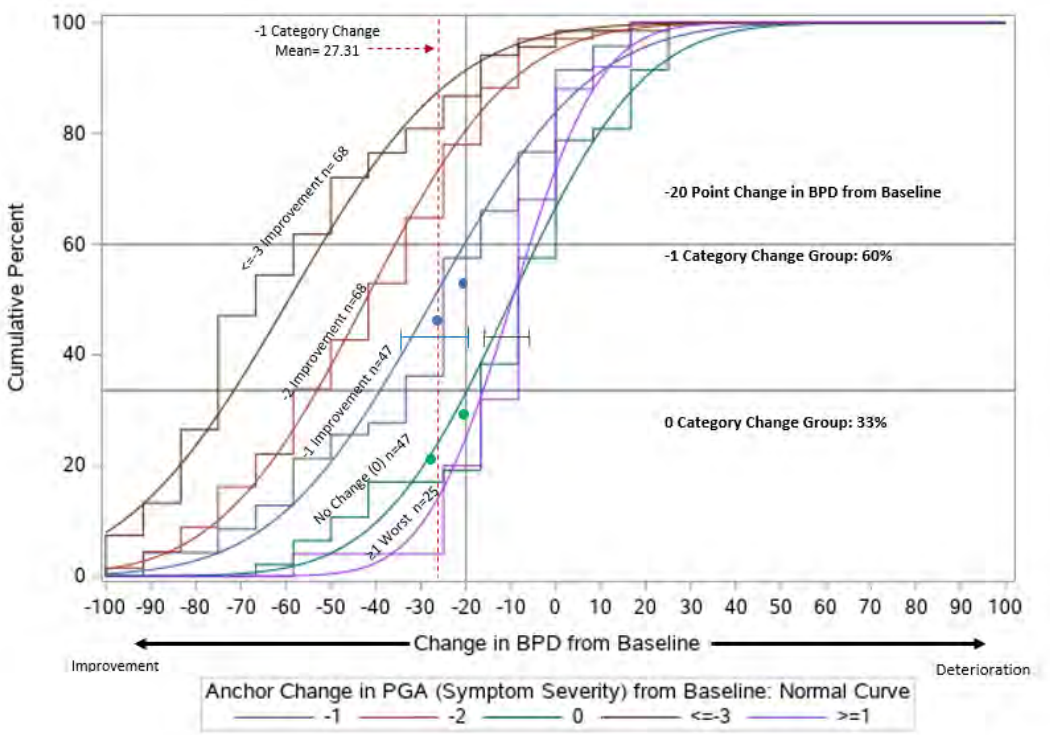
experience the improvement. As illustrated in Figure 4.3-2, approximately 35% of the "no change" group and 61% of the "1-category improvement" group experienced at least a 19-point improvement on the BPD Scale by Week 24. The high percent of patients in the "no change" group who improved on the BPD Scale by Week 24 indicates that setting the minimum meaningful change threshold at 19 points may be too liberal. The percent of misclassified responders can be improved by selecting a slightly larger value. Setting the minimum meaningful change threshold at 20-point improvement on the BPD Scale would decrease slightly the percent of misclassified responders for the "no change" group to 33% while decreasing slightly the percent of patients classified as responders to 60% for the "1-category improvement" group. As supportive information, the empirical CDFs were step-curves (reflecting the discrete nature of the BPD scores) are provided (Figure 4.3-3), indicating that smooth curves are reasonably close to the empirical CDFs.

Figure 4.3-2: Cumulative Distribution Function of Change at Week 24 in UFS-QoL BPD Scale Score by PGA Anchor Change Category (Collapsed)



Abbreviations: BPD = bleeding and pelvic discomfort; PGA = patient global assessment.

Figure 4.3-3: Empirical Cumulative Distribution Function of Change at Week 24 in UFS-QoL BPD Scale Score by PGA Anchor Change Category (Collapsed)



Abbreviations: BPD = bleeding and pelvic discomfort; PGA = patient global assessment.

4.4 Exit Interview Study Synthesis

4.4.1 Objectives

The objectives of the exit interviews were to: 1) provide qualitative evidence to understand meaningful change for patients following clinical intervention and 2) to elicit data on what patients consider to be a minimum meaningful improvement on different patient-reported outcomes (PROs), including:

- The UFS-QoL BPD Scale,
- The PGA symptoms severity.

These objectives were achieved through conducting web/Internet-based video or telephone interviews with English-speaking patients in the US within 3 to 14 days after their Week 24 visit of either ongoing phase 3 clinical study (MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]).

Minimum meaningful improvements on other PROs were also explored as part of the exit interview study; results of the respective exercises will be included in the full report for this exit interview study.

4.4.2 Methodology – Qualitative Interviews

The exit interviews were conducted via a web/Internet-based video platform (Doxy.me [https://doxy.me/]) or via telephone by trained and experienced Endpoint Outcomes interviewers.

In the event that a patient did not improve by at least 1 point from Baseline Day 1 to Week 24 based on her PGA of symptom severity scores, meaningful change exercises were not conducted for any of the PROs. An improvement on the PGA of symptom severity was required so that patients could provide contextually relevant feedback related to positive changes in uterine fibroid symptoms, as they would have experienced an improvement throughout the trial. Table 4.4-1 summarizes the measures/scales of interest, the type of data that was used in the respective meaningful change exercises, and the criteria that must have been met in order for the patient to participate in the respective meaningful change exercise.

Table 4.4-1: Overview of Procedures for Meaningful Change Exercises

Measure/Scale	Type of Data Used	Criteria That Must Have Been Met in Order to Conduct the Respective Meaningful Change Exercise
UFS-QoL BPD Scale (calculated)	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) Baseline Day 1 response	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24
PGA of symptom severity	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) responses (Baseline Day 1 and Week 24)	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24

Abbreviations: PGA = patient global assessment; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life bleeding and pelvic discomfort.

For the UFS-QoL BPD Scale, only patients' clinical study (ie, MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]) Baseline Day 1 data were used during interviews; the meaningful change discussions were hypothetical as Week 24 data were not made available to Endpoint Outcomes.[1] For the UFS-QoL BPD Scale, patients were provided with both their Baseline item-level scores and the summary score calculated based on the three items in the scale. Patients were also given a copy of the three items that comprise the UFS-QoL BPD Scale for reference during the meaningful change exercise. Patients were then presented with prespecified point change increments (ie, 10 points) and asked whether those changes reflected a meaningful improvement. If a patient indicated that a 10-point increment change would be meaningful, she was asked if an increment 5 points fewer would still be meaningful. Using a stepwise approach, interviewers then moved along the scale to identify the point at which minimum meaningful improvement was achieved for the respective patient.

For the PGA of symptom severity, patients were presented with their clinical study scores at Baseline Day 1 and Week 24 and asked if the change was meaningful. Next, patients were presented with a series of hypothetical point changes (ie, more change if the change was not

[1] For secondary endpoint data, only Baseline responses were shared with Endpoint Outcomes.

meaningful or less change if the change was meaningful, as warranted) and asked if those would be meaningful. This process continued until the minimum meaningful change on the PGA of symptom severity for that patient was identified.

Audio recordings of the interviews were transcribed verbatim and anonymized by removing identifying information such as names and places. Each transcript was considered a unit of analysis, and data from all transcripts were aggregated following coding. An initial coding scheme was developed based on the semistructured interview guide and research objectives. The coding scheme was applied and operationalized using Atlas.ti version 8.2.30 (Atlas.ti GmbH, Berlin), a software program designed specifically for qualitative data analysis. Specifically, codes were applied to selected text within each transcript and then queried for frequency across transcripts. Frequencies of patients' interview responses (eg, minimum meaningful change responses) are reported. Minimum meaningful point change medians and ranges were calculated in Excel. As the sample size for the study was small and to reduce the influence of potential outliers, the median is the preferred measure of central tendency reported.

4.4.3 Results

Thirty patients with heavy menstrual bleeding associated with uterine fibroids participated in exit interviews. The average age of these patients was 44, with ages ranging from PPD More than half of the patients (n = PPD self-reported as PPD and most patients (n = PPD were PPD In addition, the majority of patients (n = 26, 86.7%) self-reported some college or higher education as their highest education level. Two patients selected "Other" as the highest level of education and self-reported that they had medical assistant credentials.

The demographic characteristics of the patients from this exit interview study closely matched those of the LIBERTY 1 (MVT-601-3001) and LIBERTY 2 (MVT-601-3002) total sample and the LIBERTY 1 and 2 US sample (see Table 4.4-2). The average age for both the LIBERTY 1 and 2 total sample and US sample was approximately 42 years. Approximately half of participants (n = 396, 51.4%) in the total sample self-reported as black or African American, and over half of the US sample (n = 372, 63.9%) self-reported as black or African American. Additionally, most participants in both the total sample (n = 588, 76.4%) and US sample (n = 450, 77.3%) self-reported as not Hispanic or Latino. Highest level of education data was collected during patient interviews by Endpoint Outcomes; therefore, education level data for all LIBERTY 1 and 2 patients are not available.

Table 4.4-2 includes demographic data for the interviewed study sample as well as the totality of LIBERTY 1 and 2 and the US-based LIBERTY 1 and 2 sample (based on a database snapshot as of 26 Apr 2019).

Table 4.4-2: Patient Demographic Information (from Baseline MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]) and Education Information Collected during Patient Interviews

Baseline Characteristics	Exit Interview Study Sample (N = 30)	LIBERTY 1 and 2 Total Sample (N = 770)	LIBERTY 1 and 2 US Sample (N = 582)
Age (years)			
Mean (SD)	43.9 (4.5)	42.0 (5.4)	42.1 (5.2)
Range	PPD		
Race			
Black or African American	PPD	396 (51.4%)	372 (63.9%)
White		329 (44.4%)	183 (31.4%)
Ethnicity			
Not Hispanic/Latino	PPD	588 (76.4%)	450 (77.3%)
Hispanic/Latino		174 (22.6%)	130 (22.3%)
Highest level of education			
High school (no degree) or less	2 (6.7%)		
High school graduate	2 (6.7%)		
Some college (no degree)	11 (36.7%)		
Associate's degree	4 (13.3%)		
Bachelor's degree	5 (16.7%)		
Master's degree	4 (13.3%)		
Other	2 (6.7%)		

Abbreviations: SD = standard deviation.

Table 4.4-3 below summarizes the total number of exit interview study patients who completed each meaningful change exercise based on the required criteria.

Table 4.4-3: Summary of the Total Number of Exit Interview Study Patients Who Completed Each Meaningful Change Activity

Measure/Scale	Number of Exit Interview Study Patients Participating in Each Exercise (Total N = 30)[2]	Criteria that Must Have Been Met in Order to Conduct the Respective Meaningful Change Exercise
UFS-QoL BPD Scale (calculated)	25	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24
PGA of symptom severity	25	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24

Abbreviations: PGA = patient global assessment; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life bleeding and pelvic discomfort.

UFS-QoL Bleeding and Pelvic Discomfort Scale

Twenty-five patients improved from Baseline Day 1 to Week 24 on the PGA of symptom severity and participated in the UFS-QoL BPD Scale meaningful change exercise. Data for 24 patients were included in the analysis as one patient provided meaningful change exercise information that was not informative and therefore was excluded from the analysis.[3] The median minimum point change considered to be a meaningful improvement was 10 points (n = 24; range = 5 to 80). The majority of patients completing the UFS-QoL BPD meaningful change activity (n = 15, 62.5%) considered a minimum change of 5 points or 10 points as meaningful (Table 4.4-4).

[2] A total of 30 patients completed exit interviews as part of this study; however, not all 30 patients completed each meaningful change exercise as additional criteria were required in order for a patient to complete the meaningful change exercises. The numbers in this table represent the total number of exit interview patients who met the criteria for participation for the specific meaningful change exercises listed.
[3] This patient did not understand how the three items comprising the UFS-QoL BPD led to the generation of her summary score and could not describe the minimum point change needed for meaningful improvement.

Table 4.4-4: UFS-QoL BPD Scale Meaningful Improvement Results

Minimum Point Change Considered to be a Meaningful Improvement	n (%) [N = 24]
5-point change	11 (45.8%)
10-point change	4 (16.7%)
15-point change	2 (8.3%)
20-point change	0 (0.0%)
25-point change	1 (4.2%)
30-point change	1 (4.2%)
35-point change	1 (4.2%)
40-point change	1 (4.2%)
45-point change	2 (8.3%)
80-point change	1 (4.2%)
Overall point change	
Median	10
Range	5 – 80

Patient Global Assessment of Symptom Severity

Twenty-five patients improved by at least 1 point from Baseline Day 1 to Week 24 on the PGA (for symptoms) and participated in the PGA of symptom severity meaningful change exercise. All patients participating in the PGA of symptom severity meaningful change exercise (n = 25, 100.0%) reported that the actual improvement experienced during the clinical study was meaningful to them.

The median minimum point change considered to be a meaningful improvement was 1 point (n = 24; range = 1 to 3); the most frequently reported minimum meaningful improvement reported by patients was a 1-point change (n = 17, 68.0%) (Table 4.4-5).

Table 4.4-5: PGA Symptom Severity Meaningful Improvement Results

Minimum Point Change Considered to Be a Meaningful Improvement	n (%) [N = 25]
1-point change	17 (68.0%)
2-point change	7 (28.0%)
3-point change	1 (4.0%)
Overall point change	
Median	1
Range	1 – 3

4.4.4 Discussion

The exit interviews provided supportive qualitative evidence to assist in the interpretation of meaningful change in patients following clinical intervention. Patients were required to improve by at least 1 point on the PGA of symptom severity over the course of the clinical study to ensure that patients interviewed had experienced improvement and could reflect upon meaningful improvements in uterine fibroid symptoms.

The decision to use actual clinical trial data in the qualitative interviews was guided by an effort to increase the contextual relevance of each of the meaningful change activities. Providing patients with their Baseline scores for the three PROs created a unique opportunity for patients to reflect on their experience since starting treatment, thereby making the exercises more relevant to them. Further, participation in the meaningful change exercises was predicated on experiencing an improvement in uterine fibroid symptoms over the course of the study, which ensured that patients could speak to meaningful changes stemming from their personal experience. This was confirmed, as all patients participating in the PGA of symptom severity meaningful change exercise (n = 25, 100.0%) reported that the change during the trial was meaningful to them.

These qualitative findings provide patient insight which can be used to supplement psychometric analyses to determine target anchor categories (for the PGA of symptom severity) and responder definitions for the UFS-QoL BPD Scale.

4.5. Determination of Responder Threshold via Triangulation of Findings

Based on the analyses of individual patients' changes in BPD Scale scores, anchored by changes in their response to the PGA of symptom severity, a 20-point change is recommended as the minimum meaningful change threshold for defining a responder. This threshold estimation used the "1-category improvement" PGA group as the target anchor, which is a significantly separated from the "no change" group with respect to the mean change on the BPD Scale. The choice of "1-category improvement" as the target anchor is supported by the majority (17/25, 68%) of the interviewed patients in the exit interview study reporting that a 1-category improvement on the PGA of symptom severity is meaningful to them. The responder threshold of a 20-point change

on the BPD Scale score is larger than what the majority of patients in the exit interview study reported to be meaningful to them, ie, an improvement between 5- to 15-points.

In summary, based on the triangulation of findings from the anchor-based analyses supported by patients' feed-back during exit interviews, a 20-point change in the BPD Scale is proposed as the responder threshold for change in BPD Scale.

4.6. References

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APPENDIX 5. ESTIMATION OF RESPONDER THRESHOLD FOR THE UFS-QOL REVISED ACTIVITIES SCALE

5.1. Approach to Estimating the Responder Threshold of the Revised Activities Scale

The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) Revised Activities Scale includes five of the seven most relevant items pertaining to physical and social activities (Coyne 2018). These are:

During the previous 3 months, how often have your symptoms related to uterine fibroids:

- Interfered with your physical activities?
- Made you decrease the amount of time you spent on exercise or other physical activities?
- Made you feel that it was difficult to carry out your usual activities?
- Interfered with your social activities?
- Caused you to plan activities more carefully?

Response options include:

- None of the time;
- A little of the time;
- Some of the time;
- Most of the time;
- All of the time.

The summary score of the five items ranges from 0 to 100, where a lower score indicates a higher ability to do activities (ie, lower score = good) and a higher score indicates a lower ability to do activities.

Change from Baseline to Week 24 in the Revised Activities Scale score is a secondary endpoint of the pivotal studies (MVT-601-3001 and MVT-601-3002) to evaluate the treatment benefit of relugolix + E2/NETA (Group A) compared with placebo (Group C). Additionally, a responder analysis will be performed between the two groups with respect to the proportion of patients who have achieved a meaningful reduction from Baseline to Week 24 in the Revised Activities Scale.

The approach used to derive the responder threshold for improvement in the Revised Activities Scale is similar to that used for the Bleeding and Pelvic Discomfort (BPD) scale (see details in Appendix 4).

This appendix briefly describes the quantitative and supportive qualitative methods and summarizes the respective analysis results.

The meaningful change threshold is the smallest reduction in the Revised Activities Scale score that is considered meaningful by patients (Cohen, 1988; Crosby, 2003; Revicki, 2008; Wyrwich, 2013; Cappelleri, 2014; Coon, 2018). The magnitude of a meaningful change threshold depends

on the magnitude of the correlation between the change in the Revised Activities Scale score and change in anchor (ie, the Patient Global Assessment [PGA] for function anchor) as well as the variability of change on the Revised Activities Scale by improvement categories on the PGA of symptoms (described in Section 5.2.2). Several anchor-based methods will be used; however, the primary analysis will be a measure of central tendency for each improvement category (see Section 5.2.3). Anchor-based methods will use data collected on:

- The UFS-QoL Revised Activities Scale score at Baseline and Week 24; and
- The PGA of function score at Baseline and Week 24.

Results from the anchor-based analyses will be supported by qualitative data collected in a patient interview study (MVT-601-037), a substudy of the phase 3 trials, in which patients from selected sites in the United States (US) provided feedback on what they considered to be a meaningful change on the Revised Activities Scale and the PGA of function (described in Section 5.4).

5.2. Statistical Analysis Plan for Estimation of the Responder Threshold

5.2.1. Anchor and Its Correlation with UFS-QoL Endpoint

The PGA of function uses a five-point verbal rating scale and asks the patient:

> How much were your usual activities limited by uterine fibroid symptoms such as heavy bleeding over the last 4 weeks?

Response options include:

- No limitation at all
- Mild limitation
- Moderate limitation
- Quite a bit of limitation
- Extreme limitation

The categorical change from Baseline to Week 24 in PGA of function score will be derived, leading to nine possible outcomes ranging from +4 (denoting worsening) to -4 (denoting improvement). The change in PGA of function at Week 24 will be used as the anchor (see Table 5.2-1).

5.2.2. Target Anchor Category

The target anchor category is the anchor category that represents the minimum meaningful change and is used as the starting point to identify potential candidates for a meaningful change threshold. For the two pivotal studies, the target anchor category will be a one-point category improvement on the PGA of function (see Table 5.2-1), as this is typically considered as a minimal clinical important difference on a five-point Likert scale.

Table 5.2-1: Change in PGA as Anchor

Anchor	Anchor Change Category	Potential Target Anchor Change Category (To Be Used for Estimation of Meaningful Change Threshold)
Change in PGA of function	-4, -3, -2, -1 (improvement), 0 (same), +1, +2, +3, +4 (worsening)	-1-category change (improvement)

Abbreviations: PGA = patient global assessment.

5.2.3. Anchor-Based Methods

To determine the meaningful change threshold for the reduction in UFS-QoL Revised Activities Scale score, the anchor-based analyses described below will be performed.

The category (or point) change in PGA of function score will be used as the anchor to classify patients into response groups, depending on their level of change in the Revised Activities Scale from Baseline to Week 24 (see Table 5.2-1). Uncollapsed, categorical change on the PGA will range from +4 to -4. Collapsed, categorical change will be considered based on the distribution of change categories on the PGA of function. Usually, the collapsing occurs on the tails with extreme worsening (+4) or improvement (-4).

Among the anchor-based analyses described below, the within-group analysis will be primary and other analyses (including between-group analysis) are supportive.

5.2.3.1. Correlation with Anchor

Correlation between the categorical change on the PGA of function score and the change in the Revised Activities Scale score will be evaluated at Week 24, using blinded pooled data from the first third of the enrolled patients from the two pivotal studies who had completed Week 24 visits and had the corresponding PGA of function data available (denoted as the "threshold determination analysis set"). Polyserial correlation coefficient will be used with a criteria value of > 0.30 indicating meaningful correlation (Cohen, 1988; Crosby, 2003; Revicki, 2008; Cappelleri, 2014; Coon, 2018).

5.2.3.2. Within-Group Meaningful Change

The magnitude of change from Baseline to Week 24 in Revised Activities Scale score will be calculated within each anchor category group. Changes in Revised Activities Scale scores are negative for reduced ability to do activities (indicating a worse outcome) and positive for increased ability to do activities (indicating a better outcome).

Descriptive statistics (*n*, mean change, median change, 25th and 75th percentiles, standard deviation [SD], confidence interval [CI], and standardized effect size [SES]) will be reported for the changes in Revised Activities Scale scores by anchor category. The SES will be calculated for each level of anchor category group by dividing the mean change score of Revised Activities Scale from Baseline by the Baseline SD of the anchor category group. The impact of treatment will be judged based on Cohen's recommendations (1988): small change (SES = 0.20),

moderate change (SES = 0.50), and large change (SES = 0.80). Significance associated within-patient change will be evaluated using paired t-tests on the change in Revised Activities Scale score separately for each level of improvement on the anchor.

5.2.3.3. Supportive Analysis of Between Group Meaningful Change Using Analysis of Variance

Analysis of variance (ANOVA) will be used to determine whether a difference in mean change scores from Baseline to Week 24 on the Revised Activities Scale exists between the categorical change groups (or the collapsed groups, as appropriate). Providing there is a significant change in Revised Activities Scale scores between the (collapsed) anchor groups, the between-group differences will be explored. Any anchor group with at least 15 patients will be included in this analysis. An anchor group with < 15 patients (usually occurring on the tails with extreme worsening [+4] or improvement [-4]) will be collapsed with its adjacent group as appropriate. Comparison of the anchor groups of interest between the target anchor ("-1 change" category) and "0 change" category will be performed using a t-test. A statistically significant difference on the Revised Activities Scale change scores corresponding to a 1-category change on the PGA of function can be used as supportive information for estimating the meaningful change threshold.

5.2.3.4. Visualizing Cumulative Distribution Function and Probability Distribution Function Plots by Anchor Category Group

Anchor-based meaningful change will also be evaluated using cumulative distribution function (CDF) plots utilizing the Kernel smoothing for all anchor category groups, based on cumulative change in the Revised Activities Scale scores for all available changes from Baseline to Week 24. Specifically, the CDF plot for each anchor category displays the probability (presented on y-axis) of patients who have achieved a given absolute change of X or less in the Revised Activities Scale score from Baseline to Week 24 for each point change along the range of possible absolute changes (from -100 [maximum reduction] to 0 [no change] to 100 [maximum increase]) expressed on the x-axis.

Similarly, the smooth probability density function (PDF) will also be plotted for each anchor category group over the range of absolute changes in the Revised Activities Scale scores. These probabilities are plotted on the y-axis with the Revised Activities Scale change score on the x-axis.

The CDF and PDF curves are delineated by anchor improvement category (from -4 to +4) displaying the center and separation between the curve for the target anchor group and the curve for the group reporting no change on PGA of function. It is expected that the CDF curves will not cross between the change category groups (eg, monotonic increase from no change to slightly improved and moderately improved).

5.2.4. Determining a Meaningful Change Threshold Using Totality-of-Evidence Approach

The meaningful change threshold will be determined using the totality of evidence from the results of above quantitative anchor-based analyses; results from the interview study (MVT-601-037) will be used as supportive evidence.

The results of these analyses and proposed thresholds will be included into the Patient-Reported Outcome dossier to be submitted at time of filing.

5.3. Results from Anchor-Based Analyses

5.3.1. Correlation of Change in Revised Activities Scale Score with PGA of Function

Meaningful change for the UFS-QoL Revised Activities Scale was derived based on anchor-based methods, supported by CDF and PDF curves. To assess the suitability of the selected anchor, PGA of function, a polyserial correlation was calculated between change on the PGA from Baseline to Week 24 and the change from Baseline to Week 24 on the Revised Activities Scale. The change in the PGA was moderately negatively correlated (r = -0.60) with the change on the Revised Activities Scale (Table 5.3-1). Given that the PGA of function is less complex than the Revised Activities Scale, this result indicates that the PGA of function is a suitable anchor for the Revised Activities Scale.

Table 5.3-1: Summary of Change from Baseline to Week 24 in UFS-QoL Revised Activities Scale by PGA of Function Change Category (mITT Population)

PGA of Function Change Category	N = 254	Change in Revised Activities					Correlation between PGA Change and Revised Activities Change[a]
		Mean (SD)	Median	95% CI	p-value[b]	SES[c]	
4-category deterioration (+4)	**2**	5.00 (7.07)	5	-58.53,68.53	0.500	0.28	-0.60
3-category deteriorations (+3)	**2**	0	0	-	-	0.00	
2-category deteriorations (+2)	5	7.00 (22.80)	0	-21.31,35.31	0.5302	0.61	
1-category deteriorations (+1)	**22**	-1.59 (23.82)	-5	-12.15,8.97	0.7572	-0.06	
0 Category deteriorations (0)	71	11.55 (28.51)	5	4.80,**18.30**	0.0011	0.38	
1-category improvement (-1)	53	**27.92** (25.65)	**20**	**20.85**,35.00	< 0.0001	1.06	
2-category improvement (-2)	**51**	51.86 (27.60)	60	44.10,59.63	< 0.0001	2.17	
3-category improvement (-3)	**35**	56.81 (27.49)	57.50	47.50,66.11	< 0.0001	2.91	
4-category improvement (-4)	13	60.77 (31.55)	70	41.71, 79.83	< 0.0001	4.40	

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; PGA = patient global assessment; SD = standard deviation; SES = standardized effect size.
mITT is used to calculate change from Baseline score at Week 24 and includes patients from the mITT population who have available change from Baseline data at Week 24.

[a] Polyserial correlation coefficient between change in Revised Activities Scale and change in PGA of function.

[b] The p-value for each individual change group is derived from a paired (within-sample) t-test assessing the difference over time.

[c] SES calculated as the mean divided by the SD of Baseline. SES is judged as small = 0.2, moderate = 0.5, and large = 0.8 (Cohen 1988).

5.3.2. Improvement on Revised Activities Scale by PGA Change Category

Uncollapsed changes on the PGA of function were used to determine minimal meaningful improvement on the Revised Activities Scale (Table 5.3-1). Improvement on the Revised Activities Scale increased monotonically for all the categories from "no change (0)" to "1-category improvement (-1)" to "2-category improvement (-2)" with non-overlapping 95% CIs for mean change of the three groups. Table 5.3-2 shows that a one category improvement (-1) is associated with a 27.92-point mean improvement in the Revised Activities Scale score at Week 24 compared to Baseline, with a 95% CI [20.85, 35.00], a large SES = 1.06, and a median improvement of 20 points.

Table 5.3-2 highlights that the difference between the "1-category improvement" and the "no change" groups (mean =11.55 with a 95% CI of [4.80, 18.30]) was statistically significant (p = 0.0013) with a moderate SES = 0.54, which reasonably supports the notion that patients interpreted these change categories as distinct.

Table 5.3-2: Summary of Change from Baseline to Week 24 in Revised Activities Scale Between Target Anchor (-1) and No change (0) in PGA of Function (mITT Population)

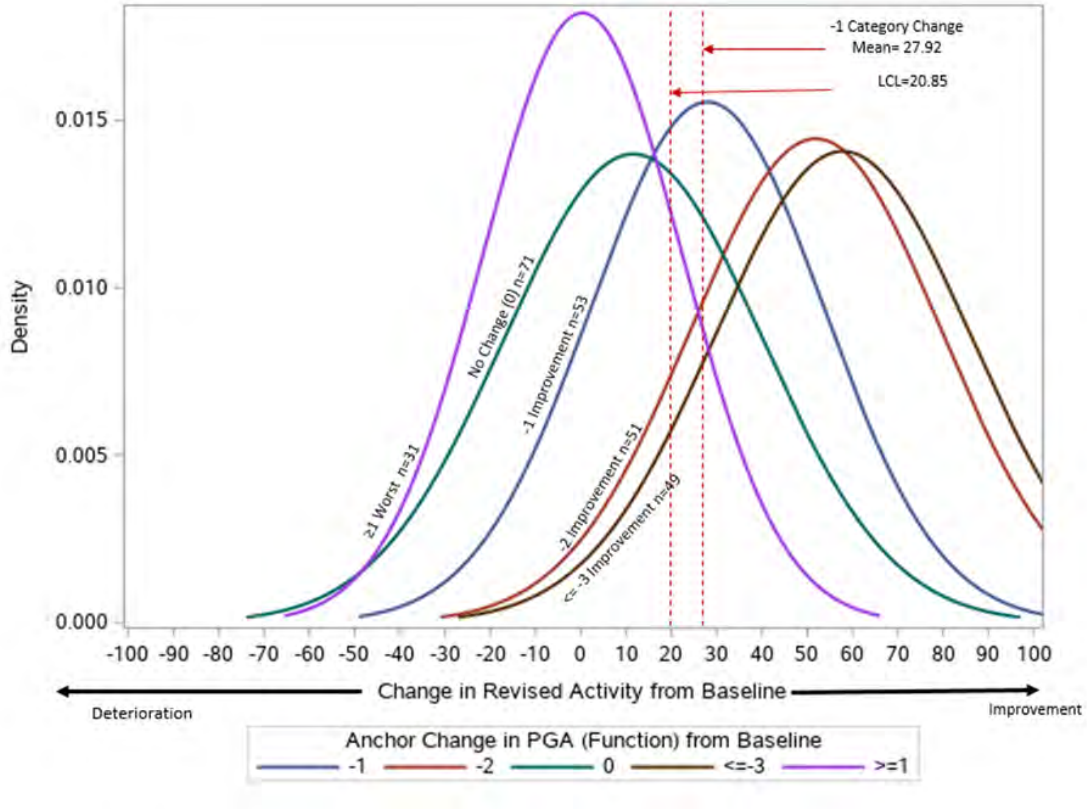
Anchor	Categorical Change	N	Mean Change from BL	SD	95% CI	p-value[a]	Baseline SD	SES
PGA	1-category improvement (-1)	53	**27.92**	**25.65**	**20.85, 35.0**			
	No change (0)	71	**11.55**	**28.51**	**4.80, 18.30**			
	Difference		**16.38**	**27.33**	**6.55, 26.20**	0.0013		0.54[b]
								0.57[c]

[a] The p-value is based on t-test for difference in mean change in BPD score between the 2 anchor groups (-1 and 0) from the ANOVA.
[b] SES calculated as the mean difference divided by the standard deviation of Baseline for no change group. They are judged as small=0.2, moderate=0.5 and large=0.8 (Cohen, 1988).
[c] SES calculated as the mean difference divided by the standard deviation of Baseline for pooled from all categories (Glass, 1976).

That patients were able to distinguish between the PGA "1-category improvement" and the 'no change" group is further supported by the nonoverlapping CIs (in Table 5.3-2) for the respective UFS-QoL Revised Activities Scale scores and as illustrated by the separation between the CDF curves presented in Figure 5.3-1. Since statistically significant differences existed in patient responses on the Revised Activities Scale between the "1-category improvement (-1) " option and the "no change" and the "2-category improvement (-2)" groups, a 1-category improvement on the PGA was considered a meaningful target anchor category for assessing the responder threshold on the Revised Activities Scale. Although a two-category improvement could have been considered for deriving the meaningful change threshold, such a threshold would not qualify as being the *minimum* threshold possible. The evidence (ie, the statistical difference between the1- and 2-category improvements and the fact that patients were able to distinguish between the two response options) supports using a 1-category improvement on the PGA of

function for estimating the minimum meaningful change threshold. This decision is also supported by qualitative evidence generated from the Exit Interview study (see Section 5.4).

Figure 5.3-1: PDF of the Change in UFS-QoL Revised Activities by PGA of Function Anchor Change Category (Collapsed)



Abbreviations: PGA = patient global assessment; LCL = lower confidence limit.

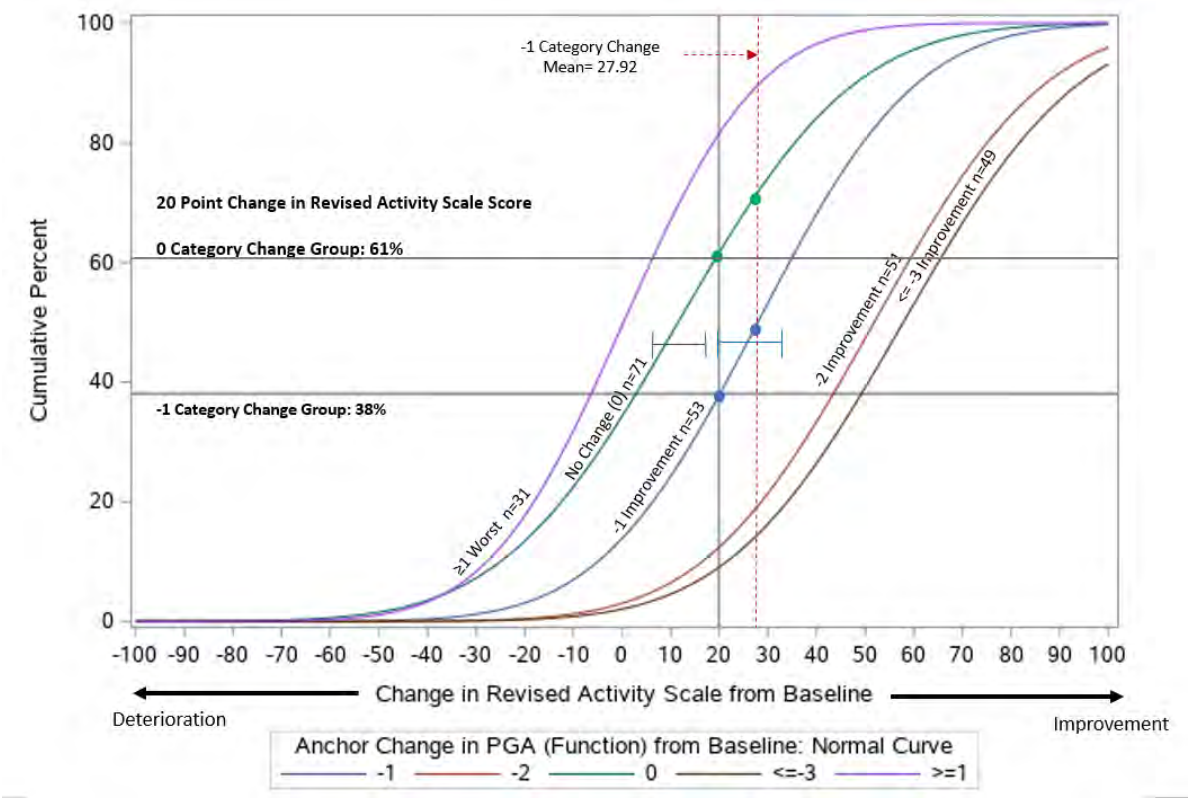
5.3.3. Estimation of Responder Threshold

Using the mean value for measuring improvement in the Revised Activities Scale would yield estimates that are conservative because expected values do not necessarily constitute a *minimum* meaningful change threshold for patients. That is, nearly half the patients stratified in the PGA "1-category improvement" who reported changes smaller than the mean on the Revised Activities Scale would be classified as nonresponders by using the mean as the threshold despite of their reporting "1-category improvement". A less conservative, though still plausible estimate for the minimal meaningful change threshold is the lower bound of the 95% CI for mean change in the "1-category improvement" group. Its use will result in a smaller proportion of patients being classified as nonresponders on the Revised Activities Scale than the expected value (ie, the mean). Similarly, one can also consider the median value since it is less influenced by outliers than either the mean or CI estimates.

According to the uncollapsed anchor-based analysis (Table 5.3-1), the median value for a "1-category improvement" is 20-points, while the lower bound 95% CI for this group is about 21-points (ie, a 21-point improvement on the revised activities between Baseline and Week 24). Given the large discrepancy between the mean and median values suggests that outliers were present in the data; hence, the median value is recommended as a potential minimum change threshold.

Examination of the CDF curves for the potential minimum meaningful threshold value of 20 points on the Revised Activities Scale allows one to estimate the cumulative percent of patients that would experience the improvement. As illustrated in Figure 5.3-2, approximately 38% of the "no change" group and 61% of the "1-category improvement" group experienced at least a 20-point improvement (eg, approximately 62% of the "no change" group and 39% of the "1-category improvement" group experienced less than a 20-point improvement to the left) on the Revised Activities Scale by Week 24.

Figure 5.3-2: Cumulative Distribution Function of Change at Week 24in UFS-QoL Revised Activities Scale Score by PGA Anchor Change Category (Collapsed)

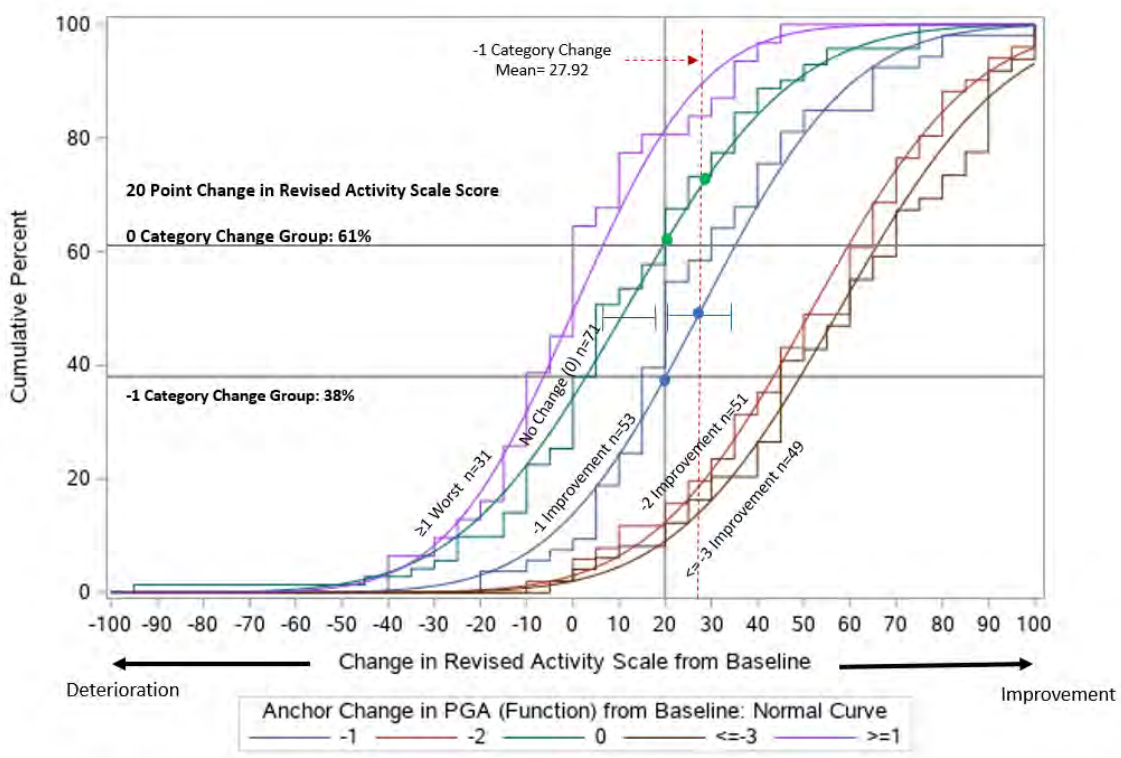


Abbreviations: PGA = patient global assessment.

As supportive information, the empirical CDFs with step-curves (reflecting the discrete nature of the revised activities scores) are provided (Figure 5.3-3), indicating that smooth curves are

reasonably close to the empirical CDFs. Examination of the PDF curves presented in Figure 5.3-1 indicates that the dispersion is roughly the same for the options between "> -3-category improvement" and "no change."

Figure 5.3-3: Empirical Cumulative Distribution Function of Change at Week 24 in UFS-QoL Revised Activities Scale Score by PGA Anchor Change Category (Collapsed)



Abbreviations: PGA = patient global assessment.

5.4. Exit Interview Study Synthesis

5.4.1 Objectives

The objectives of the exit interviews were: 1) to provide qualitative evidence to understand meaningful change for patients following clinical intervention and 2) to elicit data on what patients consider to be a minimum meaningful improvement on different patient-reported outcomes (PROs), including:

- The UFS-QoL Revised Activities Scale;
- The PGA of function.

These objectives were achieved through conducting web/Internet-based video or telephone interviews with English-speaking patients in the US within 3 to 14 days after their Week 24 visit

of either ongoing phase 3 clinical study (MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]).

Minimum meaningful improvements on other PROs were also explored as part of the exit interview study; results of the respective exercises will be included in the full report for this exit interview study.

5.4.2 Methodology – Qualitative Interviews

The exit interviews were conducted via a web/Internet-based video platform (Doxy.me [https://doxy.me/]) or via telephone by trained and experienced Endpoint Outcomes interviewers.

If a patient did not improve by at least 1 point from Baseline Day 1 to Week 24 based on her PGA of function, meaningful change exercises were not conducted for the PGA of function and the UFS-QoL Revised Activities Scale. An improvement on the PGA of function was required so that patients could provide contextually relevant feedback related to positive changes as they would have experienced an improvement throughout the trial. Table 5.4-1 summarizes the measures/scales of interest, the type of data that was used in the respective meaningful change exercises, and the criteria that must have been met in order for the patient to participate in the respective meaningful change exercise.

Table 5.4-1: Overview of Procedures for Meaningful Change Exercises

Measure/Scale	Type of Data Used	Criteria That Must Have Been Met in Order to Conduct the Respective Meaningful Change Exercise
UFS-QoL Revised Activities Scale (calculated)	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) Baseline Day 1 response	Improvement on PGA of function from Baseline Day 1 to Week 24
PGA (for function)	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) responses (Baseline Day 1 and Week 24)	Improvement on PGA of function from Baseline Day 1 to Week 24

Abbreviations: PGA = patient global assessment; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.

For the UFS-QOL Revised Activities Scale, only patients' clinical study (ie, MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]) Baseline Day 1 data were used during interviews; the meaningful change discussions were hypothetical, as Week 24 data were not made available to Endpoint Outcomes.[4] For the UFS-QoL Revised Activities Scale, patients were provided with both their Baseline item-level scores and the summary score calculated based on the five items in the scale. Patients were also given a copy of the five items that comprise the UFS-QoL Revised Activities Scale for reference during the meaningful change exercise. Patients were then presented with pre-specified point change increments (ie, 10 points) and asked whether those changes reflected a meaningful improvement. If a patient indicated that a 10-point

[4] For secondary endpoint data, only Baseline responses were shared with Endpoint Outcomes.

increment change would be meaningful, she was asked if an increment 5 points fewer would still be meaningful. Using a stepwise approach, interviewers then moved along the scale to identify the point at which minimum meaningful improvement was achieved for the respective patient.

For the PGA of function, patients were presented with their clinical study scores at Baseline Day 1 and Week 24 and were asked if the change was meaningful. Next, patients were presented with a series of hypothetical point changes (ie, more change if the change was not meaningful or less change if the change was meaningful, as warranted) and asked if those would be meaningful. This process continued until the minimum meaningful change on the PGA of function for that patient was identified.

Audio-recordings of the interviews were transcribed verbatim and anonymized by removing identifying information such as names and places. Each transcript was considered a unit of analysis, and data from all transcripts were aggregated following coding. An initial coding scheme was developed based on the semi-structured interview guide and research objectives. The coding scheme was applied and operationalized using Atlas.ti version 8.2.30 (Atlas.ti GmbH, Berlin), a software program designed specifically for qualitative data analysis. Specifically, codes were applied to selected text within each transcript and then queried for frequency across transcripts. Frequencies of patients' interview responses (eg, minimum meaningful change responses) are reported. Minimum meaningful point change medians and ranges were calculated in Excel. As the sample size for the study was small and to reduce the influence of potential outliers, the median is the preferred measure of central tendency reported.

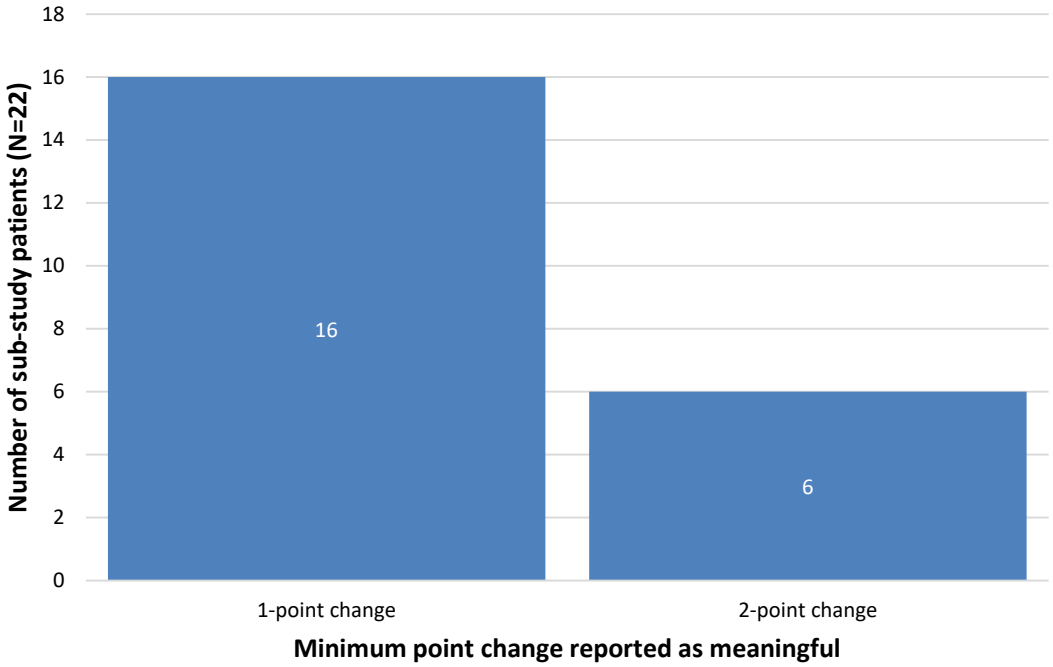
5.4.3 Results

5.4.3.1 PGA of Function[5]

Twenty-two patients improved from Baseline Day 1 to Week 24 on the PGA of function and participated in the PGA of function meaningful change exercise. The demographic characteristics of the 22 patients who completed the PGA of function closely match that of the entire substudy sample as the sample was mostly PPD (n = PPD PPD (n = PPD had completed at least some college or higher (n = 19, 86.4%), and had an average age of approximately 44 years. The median minimum point change considered to be a meaningful improvement was 1 point (n = 22, range = 1-2); the most frequently reported minimum meaningful improvement reported by patients was a 1-point change (n = 16, 72.7%) (Figure 5.4-1).

[5] The PGA of function asks: How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? Response options include: No limitation at all, mild limitation, moderate limitation, quite a bit of limitation, and extreme limitation.

Figure 5.4-1: Meaningful Change Estimation: Results of the PGA (for Function)



5.4.3.2 UFS-QoL Revised Activities Subscale[6]

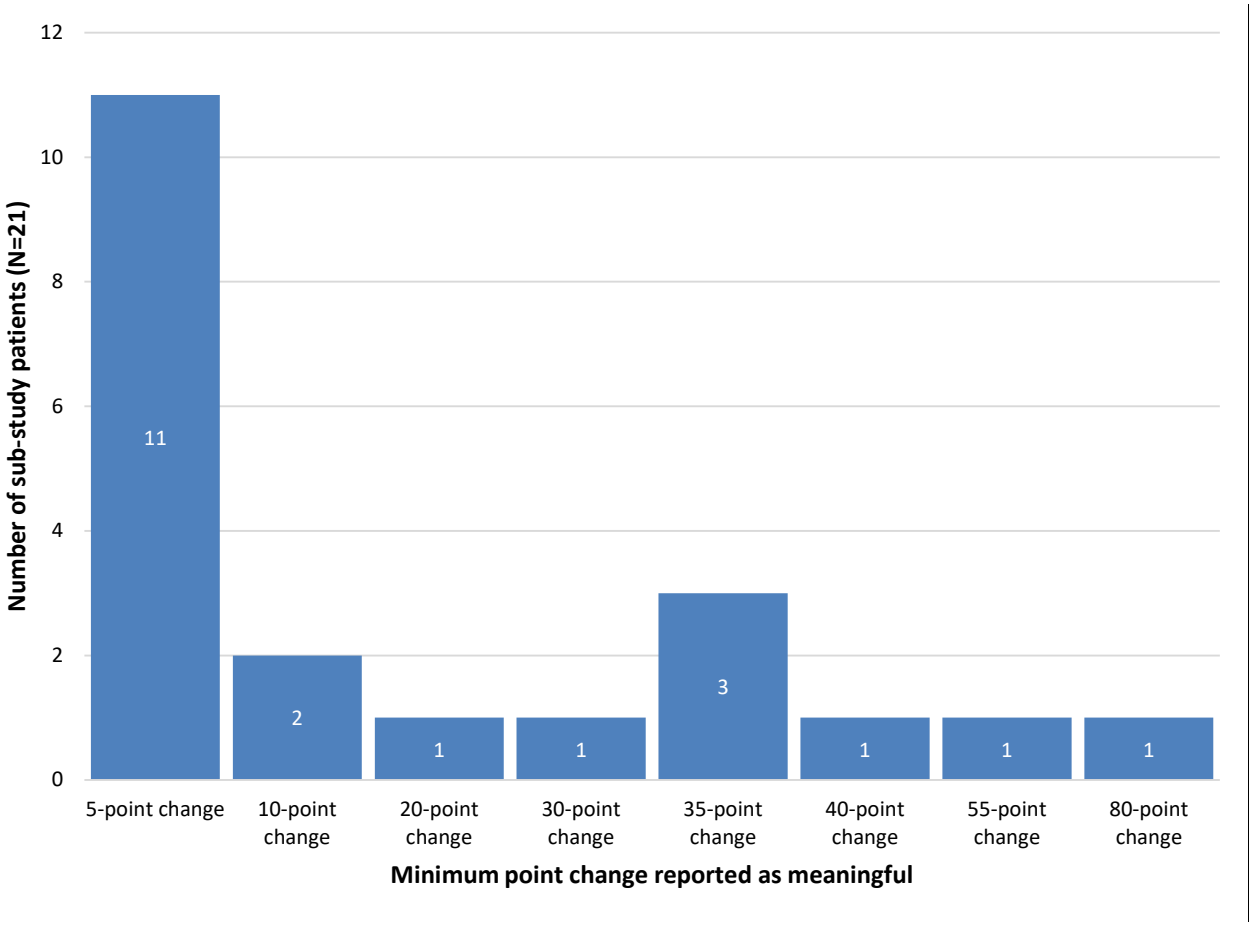
Twenty-two patients improved from Baseline Day 1 to Week 24 on the PGA of function and participated in the UFS-QoL revised activities subscale meaningful change exercise. Data for 21 patients were included in the analysis as one patient provided meaningful change exercise information that was not informative and therefore was excluded from the analysis.[7] The demographic characteristics of the 21 patients who completed the UFS-QoL Revised Activities Scale closely match that of the entire substudy sample as the sample was mostly PPD (n = PPD (n = PPD had completed at least some college or higher (n = 19, 90.5%), and had an average age of approximately 44 years.

[6] The UFS-QoL revised activities subscale includes five items, which ask: During the previous 3 months, how often have your symptoms related to uterine fibroids … 11) interfered with your physical activities; 13) made you decrease the amount of time you spent on exercise or other physical activities; 19) made you feel it was difficult to carry out your usual activities; 20) interfered with your social activities; and 27) made you plan activities more carefully. Response options include 1) None of the time, 2) A little of the time, 3) Some of the time, 4) Most of the time, and 5) All of the time. The score range for the subscale is 0-100. A higher score on the revised activities subscale indicates a lower interference in activities while a lower score on the subscale indicates a higher interference in activities.

[7] This patient was unwilling to describe the minimum point change needed for meaningful improvement for the UFS-QoL revised activity subscale.

The median minimum point change considered to be a meaningful improvement was 5 points (n = 21, range = 5-80); the most frequently reported minimum meaningful improvement reported by patients was a 5-point change (n = 11, 52.4%) (Figure 5.4-2).

Figure 5.4-2: Meaningful Change Estimation: Results of the UFS-QoL Revised Activities Subscale



5.5. Determination of Responder Threshold via Triangulation of Findings

Based on the analyses of individual patient's change in Revised Activities Scale scores anchored by change in their response to the PGA of function, a 20-point change is recommended as the minimum meaningful change threshold for defining a responder. This threshold estimation used the "1-category improvement" PGA group as the target anchor, which is significantly separated from the "no change" group with respect to the mean change on the Revised Activities Scale. The choice of "1-category improvement" as the target anchor is supported by the majority (16/22, 73%) of the interviewed patients in the exit interview study reporting that a 1-category improvement on the PGA of function is meaningful to them. The responder threshold of a 20-point change on the Revised Activities Scale score is larger than what the majority of patients in the exit interview study reported to be meaningful to them (ie, improvements of 5 points [11/21] and 10 points [2/21]).

In summary, based on the triangulation of findings from the anchor-based analyses supported by patients' feedback during exit interviews, a 20-point change in the Revised Activities Scale is proposed as the responder threshold for change in Revised Activities Scale.

5.6. References

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STATISTICAL ANALYSIS PLAN

Study Titles:	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3001 and MVT-601-3002
Indication:	Heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	IND # 131161 EudraCT # 2016-003727-27
Version/Effective Date:	07-May-2019

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

MVT-601-3001 (LIBERTY 1): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

MVT-601-3002 (LIBERTY 2): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

This statistical analysis plan has been approved by Myovant Sciences GmbH ("Myovant"), with Myovant Sciences, Inc., acting as agent of Myovant. The following signatures document this approval.

PPD

07 May 2019
Date

07 May 2019
Date

07 May 2019
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07 MAY 2019
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LIST OF ABBREVIATIONS

Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMD	bone mineral density
BMI	body mass index
C_τ	predose trough concentrations
CDF	cumulative distribution function
CFI	comparative fit index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DSMB	data safety monitoring board
DXA	dual-energy x-ray absorptiometry
E2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOT	end-of-treatment
EQ-5D-5L	European Quality of Life Five-Domain Five-Level
FP	feminine product
FPRR	feminine product return rate
FSH	follicle-stimulating hormone
GFI	goodness of fit index
Hgb	hemoglobin
ICH	International Council on Harmonisation
ITT	intent-to-treat
KM	Kaplan Meier
LH	luteinizing hormone
LLN	lower limit of normal
LS	least squares
max	maximum
MBL	menstrual blood loss
min	minimum
mITT	modified intent to treat

Term	Definition/Explanation
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
M-vol	myoma volume
NET	norethindrone
NETA	norethindrone acetate
NRS	Numerical Rating Scale
PBO	placebo
PDF	probability density function
PGA	patient global assessment
PK	pharmacokinetic
PT	Preferred Term
QD	once daily
QTcF	corrected QT interval Fridericia
RMSEA	root mean square error of approximation
SAP	statistical analysis plan
SD	standard deviation
SES	standardized effect size
SMQ	standard MedDRA query
SOC	System Organ Class
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
U-vol	uterine volume
WHO	World Health Organization
Wks	weeks

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the analyses planned for phase 3 studies MVT-601-3001 (LIBERTY 1) and MVT-601-3002 (LIBERTY 2), both entitled "An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids." In these studies, patients are randomized to one of three treatment arms: relugolix 40 mg + estradiol/norethindrone acetate (E2/NETA) 1 mg/0.5 mg for 24 weeks (Group A, also referred to as the relugolix + E2/NETA group), relugolix 40 mg for 12 weeks followed by 12 weeks of relugolix 40 mg + E2/NETA 1 mg/0.5 mg (Group B, also referred to as the relugolix + delayed E2/NETA group), or placebo for 24 weeks (Group C, also referred to as the placebo group).

The 2 phase 3 studies are replicative; the only difference between the two protocols is the Week 24 endometrial biopsies, which in MVT-601-3001 are done in all patients and in MVT-601-3002 depend on the results of the Week 24 ultrasound.

This SAP was developed in accordance with the International Council on Harmonisation (ICH) E9 guidelines. All decisions regarding statistical analysis of the study, as defined in this SAP, will be made prior to unblinding of the study data.

The SAP is based on:

- Protocol MVT-601-3001, Amendment 2, dated 18 Sept 2017;
- Protocol MVT-601-3002, Amendment 2, dated 25 Sept 2017;
- ICH guidelines E3 (Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

This document may evolve over time (eg, to reflect the requirements of protocol amendments or regulatory requests). However, the SAP is to be finalized, approved by the sponsor, and placed on file before the database is locked. Changes to the final approved plan will be noted in the clinical study report (CSR). Unless otherwise specified, the objectives, definitions of endpoints, and pre-specification of analyses presented in this document apply to both studies.

1.1. Study Objectives and Endpoints

The study objectives and corresponding endpoints are listed in the following table. The endpoints in *italics* are not listed in the protocol, but they have been identified as important for assessment of treatment effect on the basis of emerging data and clinical relevance to the study objectives and therefore are included in this SAP.

Table 1: Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary Efficacy	
To determine the benefit of relugolix 40 mg once daily co-administered with E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids	Proportion of women in the relugolix + E2/NETA group versus the placebo group who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method
Key Secondary Efficacy (Alpha-Protected for Hierarchical Hypothesis Testing — relugolix + E2/NETA versus placebo)	
Achievement of amenorrhea	Proportion of women who achieve amenorrhea over the last 35 days of treatment
Heavy menstrual bleeding associated with uterine fibroids	Percent change from Baseline to Week 24 in MBL volume
Impact of uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the UFS-QoL	*Change from Baseline to Week 24 in the UFS-QoL Bleeding and Pelvic Discomfort Scale score, a sub-scale of the UFS-QoL Symptom Severity scale*
Change in hemoglobin	*Proportion of women with a hemoglobin ≤ 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline to Week 24*
Pain associated with uterine fibroids	*Proportion of patients with a maximum NRS score ≤ 1 during the last 35 days before the last dose of study drug in the subset of women with a maximum NRS score ≥ 4 for pain associated with uterine fibroids during the last 35 days prior to randomization*
Uterine fibroid volume	Percent change from Baseline to Week 24 in uterine fibroid volume
Uterine volume	Percent change from Baseline to Week 24 in uterine volume
Other Secondary Efficacy (Not for Hierarchical Hypothesis Testing) [a]	
To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids	Proportion of women in the relugolix + delayed E2/NETA group versus the placebo group who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method
Heavy menstrual bleeding associated with uterine fibroids	• *Percent change from Baseline in MBL volume by visit* • *Change from Baseline in MBL volume by visit*

Objective(s)	Endpoint(s)
	• Time to achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume as measured by the alkaline hematin method • *Proportion of women in the relugolix + E2/NETA group versus the placebo group who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume by visit*
Achievement of amenorrhea	• *Sustained amenorrhea rate by visit* • *Time to achieving sustained amenorrhea* • *Time to achieving amenorrhea*
Change in hemoglobin	• Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24 • *Change from Baseline to Week 24 in hemoglobin for women with a hemoglobin ≤ 10.5g/dL at Baseline*
Impact of uterine fibroids on symptoms, activities and health-related quality of life as measured by components of the UFS-QoL	• Change from Baseline to Week 24 in the UFS-QoL Symptom Severity Scale score • Change from Baseline to Week 24 in the UFS-QoL Activities Scale score • *Change from Baseline to Week 24 in the UFS-QoL Revised Activities Scale score* • *Proportion of responders who achieved a meaningful increase of at least 20 points from Baseline to Week 24 in UFS-QoL Revised Activities Scale score* • *Proportion of responders who achieved a meaningful reduction of at least 20 points from Baseline to Week 24 in UFS-QoL Bleeding and Pelvic Discomfort Scale score* • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QoL Question 11 • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QoL Question 20

Objective(s)	Endpoint(s)
	• Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QoL Question 29
Patient global assessment for function and symptoms as measured by the PGA for function and symptoms	• Change in PGA for uterine fibroid related function from Baseline to Week 24 • Change in PGA for uterine fibroid symptoms from Baseline to Week 24 • *Proportion of patients achieving improvement from Baseline in PGA for uterine fibroid symptoms from Baseline to Week 24* • *Proportion of patients achieving improvement from Baseline in PGA for uterine fibroid related function from Baseline to Week 24*
Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire	• Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities
Pain associated with uterine fibroids[b]	Proportion of women who achieve a *maximum* NRS score for pain associated with uterine fibroids over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization
Safety	
To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks	Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms
To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in the relugolix + E2/NETA group compared with the relugolix + delayed E2/NETA group in women with heavy menstrual bleeding associated with uterine fibroids	Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in the relugolix + E2/NETA group compared with relugolix + delayed E2/NETA group as assessed by DXA

Objective(s)	Endpoint(s)
To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks	Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA
To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg in women with heavy menstrual bleeding associated with uterine fibroids	Incidence of vasomotor symptoms
Pharmacokinetic and Pharmacodynamic	
To evaluate the pharmacokinetic and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg	• Predose trough concentrations (C_τ) of relugolix, and NET and Baseline-adjusted E2 concentration • Absolute and changes from Baseline to Week 24 in predose concentrations of LH, FSH, E2, and progesterone
Exploratory	
To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of E2 1 mg and NETA 0.5 mg compared with placebo on patient-reported quality of life outcome measures (EQ-5D-5L)	Change from Baseline to Week 24 in the EQ-5D-5L Scale score

Abbreviations: DXA, dual energy x-ray absorptiometry; E2, estradiol; EQ-5D-5L, European Quality of Life Five-Domain Five-Level; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MBL, menstrual blood loss; NET, norethindrone; NETA, norethindrone acetate; NRS, numerical rating scale; PGA, Patient Global Assessment; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life.

[a] The secondary endpoints below will be assessed comparing the relugolix + E2/NETA group with the placebo group inferentially; the relugolix + E2/NETA group to the relugolix + delayed E2/NETA group and the relugolix + delayed E2/NETA group to the placebo group descriptively, unless otherwise specified.

[b] Changed from mean NRS score (in the protocol) to maximum NRS score. Since pain associated with uterine fibroids is mostly during menstrual days, mean NRS scores over the last 35 days is very low (< 1) for most patients, hence, not appropriate to define percent reduction from Baseline.

2. STUDY DESIGN

2.1. Summary of Study Design

The LIBERTY 1 and LIBERTY 2 studies are two replicate, randomized, double-blind, placebo-controlled phase 3 studies evaluating the efficacy and safety of relugolix 40 mg in combination with E2 1 mg/NETA 0.5 mg in women with heavy menstrual bleeding associated with uterine fibroids (MVT-601-3001, MVT-601-3002). Patients with heavy menstrual bleeding associated with uterine fibroids — as evidenced by a menstrual blood loss (MBL) volume of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during one cycle, as measured by the alkaline hematin method during the screening period — who met other eligibility criteria were randomly assigned (1:1:1) to 1 of the 3 treatment arms:

- Group A (relugolix + E2/NETA): relugolix 40 mg once daily co-administered with E2 1 mg/NETA 0.5 mg for 24 weeks;
- Group B (relugolix + delayed E2/NETA): relugolix 40 mg once daily for 12 weeks followed by relugolix 40 mg once daily co-administered with E2 1 mg/NETA 0.5 mg for 12 weeks;
- Group C (placebo): placebo for 24 weeks

Randomization was stratified as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening MBL volume using alkaline hematin method: < 225 mL versus ≥ 225 mL.

The primary endpoint for both trials is the proportion of women receiving relugolix + E2/NETA (Group A) versus placebo (Group C) who achieve BOTH a MBL volume of < 80 mL AND at least a 50% reduction from Baseline in MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method.

This study includes a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a safety follow-up period (~30 days). During the screening period, diagnoses of uterine fibroids are confirmed by centrally reviewed transvaginal ultrasound. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during the screening period are treated with oral or parenteral iron replacement therapy. After randomization, patients begin double-blinded study drug treatment for 24 weeks.

Patients who complete LIBERTY 1 or LIBERTY 2, including those randomized to placebo, and who meet other eligibility criteria are offered the opportunity to enroll in a 28-week open-label extension study, in which all patients will receive relugolix 40 mg co-administered with E2 1 mg and NETA 0.5 mg. Patients who do not enroll into the extension study have a safety follow-up visit approximately 30 days after their last doses of study medication.

Additional safety follow-up may be performed after the safety follow-up visit. Data collected during the additional safety follow-up period will be summarized and reported in an addendum to the respective clinical study report. Patients who are not proceeding into the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy should be treated as per standard of care and additional follow-up should be evaluated and managed, as

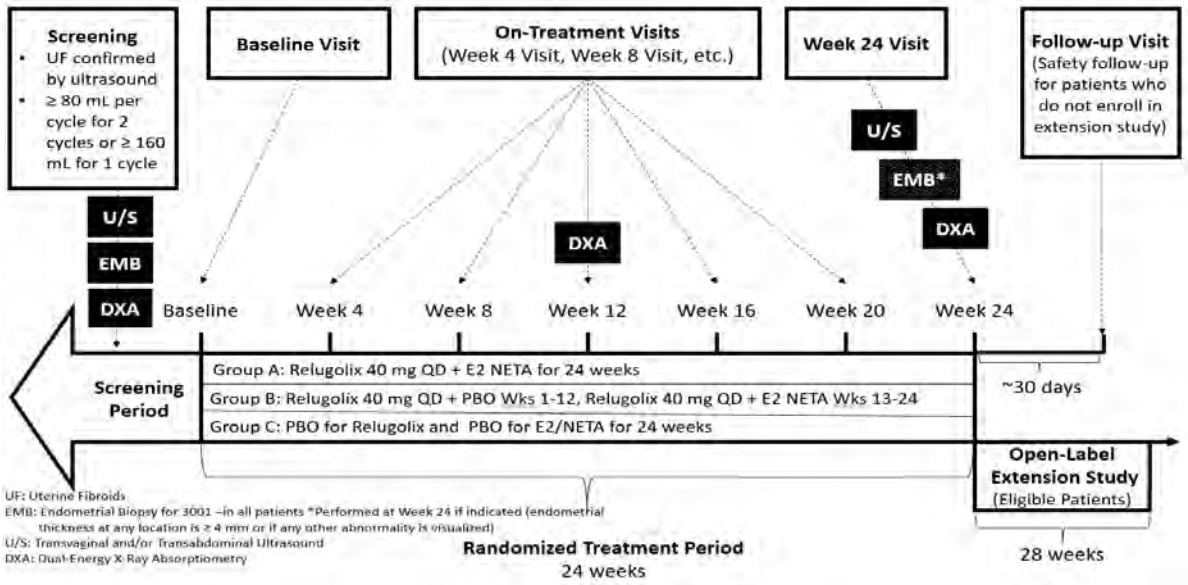
needed, by a gynecologist. In addition, they should undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory.

Patients who are not proceeding into the extension study and who have a bone mineral density (BMD) loss of > 2% at the lumbar spine (L1–L4) or total hip relative to the Baseline measurement at their Week 24/Early Termination visit will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc.) that might affect BMD through the time of the repeat DXA scan. If the DXA scan 6 months post-treatment continues to show BMD loss of > 1.5% at the lumbar spine and/or > 2.5% at the total hip compared with Baseline, patients will have an additional scan at 12 months post-treatment. All follow-up DXA scans will be submitted for central reading. Patients whose menses had not resumed as of the safety follow-up visit for unexplained reasons will be contacted by telephone to determine if menses have resumed. Patients with reductions in visual acuity will be referred for ophthalmology consultation.

An external independent data and safety monitoring board (DSMB) was established to review periodic safety analyses, including BMD assessments. The roles and responsibilities of the independent DSMB are described in a separate charter. A separate SAP was created to document the specific safety data analyses that would be performed by an independent data coordinating center for the DSMB on an ongoing basis during the study.

A schematic of the study is presented in Figure 1.

Figure 1: Study Schematic



Abbreviations: E2, estradiol; NETA, norethindrone; PBO, placebo; QD, once daily; Wks, weeks.

2.2. Sample Size Considerations

2.2.1. Sample Size Justifications for Primary Efficacy Endpoint

The following assumptions were used to determine the sample size for this study:

- 2-sided type I error rate: 0.05
- Randomization: 1:1:1
- Responder rate for placebo group: 25%
- Difference in responder rates between the relugolix + E2/NETA group and the placebo group: 30%
- Dropout rate: ~20%

With the assumption of a dropout rate of 20%, approximately 130 women in the relugolix + E2/NETA group and 130 women in the placebo group will provide at least 99% power at a 2-sided 0.05 significance level to detect a 30% difference in responder rates between relugolix + E2/NETA group and the placebo group for the primary endpoint. With an additional 130 women in the relugolix + delayed E2/NETA group, the total sample size will be approximately 390 women.

The assumed responder rate of 25% for the placebo group is within the range of responder rates observed from similar phase 3 trials in uterine fibroids (Stewart, 2017). The sample size and power calculations are based on a chi-squared test.

2.2.2. Sample Size Justifications for Percent Change in Bone Mineral Density at 12 Weeks

A pooled analysis of the percent change in BMD at 12 weeks using data from both phase 3 studies is described separately in the statistical analysis plan for the Integrated Summary of Safety. The results of this pooled analysis comparing the relugolix + E2/NETA group with the relugolix + delayed E2/NETA group will be presented in the Integrated Summary of Safety and will not be included in the CSRs for these studies.

For the comparison of the relugolix + E2/NETA group with the relugolix + delayed E2/NETA group with respect to the percent change in BMD from Baseline to Week 12 at the lumbar spine (L1–L4), approximately 260 women in the relugolix + E2/NETA group (pooled between the LIBERTY 1 and LIBERTY 2 studies) and 260 women in the relugolix + delayed E2/NETA (pooled) will provide at least 90% power at a 2-sided 0.05 significance level to detect a 1.25% absolute treatment difference, assuming a standard deviation of 4% and up to 15% dropout rate for each treatment group. Power calculations for this BMD comparison are based on a two-sample t-test.

Sample size and power calculations were performed using the software package *nQuery* 4.0 (Statistical Solutions Ltd.).

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim efficacy analyses were planned or performed for these two studies.

An external, independent DSMB was established to review periodic safety analyses, including BMD assessments. A separate SAP was created to document the specific safety data analyses that would be performed by an independent data coordinating center for the DSMB on an ongoing basis during the study.

3.2. Final Analyses

The final analysis of all efficacy and safety data from MVT-601-3001 and MVT-601-3002 will occur after approximately 390 patients have been randomized to each study and have had the opportunity to be followed for 24 weeks of study treatment and through the 30-day safety follow-up visit. This document describes this final analysis.

There will be periodic safety data review by the DSMB. An independent data coordinating center has performed the periodic safety analyses and has provided results of these analyses to the DSMB, as defined in the DSMB charter and outlined in a separate DSMB SAP.

3.3. Safety Follow-Up Analyses

Patients who are not proceeding into the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy should be treated as per standard of care and additional follow up should be evaluated and managed, as needed, by a gynecologist. In addition, they should undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory.

Patients who are not proceeding into the extension study and who have a BMD loss of > 2% at the lumbar spine (L1–L4) or total hip relative to the Baseline measurement at their Week 24/Early Termination visit will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scan. If the DXA scan 6 months post-treatment continues to show BMD loss of > 1.5% at the lumbar spine and/or > 2.5% at the total hip compared to Baseline patients will have an additional scan at 12 months post-treatment. All follow-up DXA scans will be submitted for central reading. Patients whose menses had not resumed as of the safety follow-up visit for unexplained reasons will be contacted by telephone to determine if menses have resumed. Patients with reductions in visual acuity will be referred for ophthalmology consultation.

Data collected during the additional safety follow-up period will be summarized and reported in an addendum to the respective clinical study report.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING OF MISSING DATA

4.1. Data Presentation Conventions

All statistical analyses will be conducted using SAS® Version 9.2 or higher.

A statistical test for the primary and secondary efficacy endpoints will be assessed at a two-sided $\alpha = 0.05$ significance level, and all confidence intervals (CIs) will be reported as two-sided unless otherwise stated.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. For continuous variables, the number of patients with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values will be tabulated.

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value; if the measured value is large (eg, > 100), fewer decimal places may be displayed.
- Percentages will be rounded to 1 decimal place;
- p-values will be rounded to 4 decimal places. p-values < 0.0001 will be presented as "< 0.0001" and p-values > 0.9999 will be presented as "> 0.9999";
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded to 1 decimal place;
- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded to 1 decimal place;
- Age will be calculated using the date of randomization. If only year of birth is collected, 1 July of the year of birth will be used to calculate age.
- 1 pound = 0.454 kg;
- 1 inch = 2.54 cm;
- Missing efficacy or safety data will not be imputed unless otherwise specified;
- For laboratory results above or below sensitivity limits displayed as "<" or ">" a quantification threshold, 0.0000000001 will be subtracted or added, respectively, to the threshold to derive a numeric result for analyses;
- For MBL volume reported as below the limit of quantification (for example, MBL below Quantification Level <5.0 mL or <2.5 mL), 0.0000000001 will be subtracted from the reported quantification threshold for the visit to derive a numeric result for analyses;
- For safety analyses, calculation of percentages will be calculated on the basis of the number of patients in the analysis population in each treatment group;

- For by-visit observed data analyses, calculation of percentages will be calculated on the basis of the number of patients with non-missing data as the denominator, unless otherwise specified;
- For other continuous endpoints, the summary statistics will include mean, SD, median, and range (minimum and maximum);
- For time-to-event endpoints, the summary statistics will include median time to event-free survival, 25th and 75th percentiles and number of patients at risk at specified time points;
- For categorical endpoints, the summary statistics will include counts and percentages;
- Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, exact methods will be employed, unless otherwise specified.

4.2. Analysis Populations

Three analysis populations are defined below. Number and percent of patients meeting the definition of each analysis population will be summarized by treatment group.

4.2.1. Modified Intent-to-Treat Population

Efficacy analyses will be performed using the modified Intent-to-Treat (mITT) population, unless otherwise specified. The mITT population is defined as all randomized patients who have received any amount of study drug (relugolix/placebo or E2/NETA/placebo). Efficacy analyses will be performed by treatment group as randomized.

4.2.2. Per-Protocol Population

The Per-Protocol population will consist of those members of the mITT population who do not have any of the specified subset of important protocol deviations (see Section 5.3).

The Per-Protocol population will not be analyzed if this population comprises > 95% or < 50% of the mITT population. The Per-Protocol population will be used for sensitivity analysis of the primary efficacy endpoint. The Per-Protocol population and the associated subset of important protocol deviations will be identified prior to unblinding the trial.

4.2.3. Safety Population

Safety analyses will be performed using the Safety population unless otherwise specified. The Safety population is the same as the mITT population and is defined as all randomized patients who have received any amount of study drug. Safety data will be analyzed by treatment group according to the actual treatment received (not the randomized treatment). Any patient who received at least one dose of relugolix will be considered as a relugolix patient.

4.3. Definitions, Computation, and Convention

4.3.1. Definition of Date of First Dose and Date of Last Dose of Study Drug

The date of the first dose of study drug is defined as the date when a patient receives the first dose of study drug (relugolix/placebo or E2/NETA/placebo). The date of the last dose of study

drug is defined as the date a patient receives the last dose of study drug. If the complete date of last dose of study drug is unknown, the last date the study drug was known to have been taken will be used.

4.3.2. Study Day

Study day will be calculated with respect to the date of the first dose of study drug (Study Day 1). For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as:

(Assessment date – date of first dose of study drug) + 1

For assessments conducted before the date (and time) of the first dose of study drug, study day will be calculated as:

(Assessment date – date of first dose of study drug)

For patients who do not receive any amount of study drug, study day will be calculated as above with respect to the date of randomization.

4.3.3. Definition of Treatment Duration

Treatment duration is defined as the duration of time from the date of the first dose of study drug to the date of the last dose of study drug as follows:

(Date of last dose of study drug – Date of first dose of study drug) + 1

For patients without complete date of last dose of study drug, the last date study drug was known to have been taken will be used to calculate treatment duration. For patients who did not return for the Early Termination visits, the time after their last visit will not be included in calculations of treatment duration.

4.3.4. Definition of Baseline Value and Post-Baseline Value

Unless otherwise specified, Baseline values are defined as the last measurement before the first administration (date and time) of study drug. A post-Baseline value is defined as a measurement taken after the first administration of study drug. Change from Baseline is defined as (post-Baseline value – Baseline value). Both date and time of study drug administration and measurement will be considered when calculating Baseline value. If the time is not available, then the date alone will be used. For patients who receive no study medication, the date of randomization will be used in place of the date of first dose in determining Baseline and post-Baseline values.

4.3.5. Visit Windows

Visit windows, which will be used to associate assessments with a scheduled visit, will be used only for summarizing data by visit. The windows for scheduled assessments are shown in Table 2, Table 3 (electrocardiogram [ECG], BMD, Uterine Fibroid Symptom and Health-Related Quality of Life [UFS-QoL]), and Table 4 (transvaginal ultrasound, endometrial biopsy, and European Quality of Life Five-Domain Five-Level [EQ-5D-5L]), respectively. For both efficacy and safety assessments, the study day will be used to determine the associated visit window.

The data collected in the electronic diary (eDiary) related to bleeding and use of feminine products will be assigned to visit windows as specified in Table 5 and will be used to calculate the feminine product return rate (FPRR) as specified in Section 7.3.3.

If the results from more than one monthly or Week 12/Week 24 assessment are within a given visit window, the non-missing result from the assessment closest to the target date will be used. If two assessments are equally close to the target day, the earlier assessment will be used. For summaries of shift from Baseline in safety parameters, all values will be considered for these analyses.

Table 2: Visit Windows for Monthly Assessments

Visit	Start Day	Target Day	End Day
Week 4[a]	1	29	43
Week 8	44	57	71
Week 12	72	85	99
Week 16	100	113	127
Week 20	128	141	155
Week 24	156	169	196
Safety Follow-Up[b]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

[a] Start day of Week 4 for study day 1 includes only post-Baseline assessments that occurred after the first dose.

[b] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids.

Table 3: Visit Windows for Week 12/Week 24 Assessments (ECG, BMD, UFS-QoL)

Visit	Start Day	Target Day	End Day
Week 12	64	85	106
Week 24	148	169	196
Safety Follow-up[a]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

Abbreviations: BMD, bone mineral density; ECG, electrocardiogram; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life.

[a] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids

Table 4: Visit Windows for Week 24 Assessments (Transvaginal Ultrasound, Endometrial Biopsy, EQ-5D-5L)

Visit	Start Day	Target Day	End Day
Week 24	128	169	196
Safety Follow-up[a]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

Abbreviations: EQ-5D-5L, European Quality of Life Five-Domain Five-Level.

[a] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids.

Table 5: Time Window for eDiary and Feminine Product Collection

Visit	Feminine Product Collection Visit Date[a,b]	Time Window[a]
Week 4	X_1	(Date of Study Day 1) - < X_1
Week 8	X_2	(X_1 +1) - ≤ X_2
Week 12	X_3	(X_2 +1) - ≤ X_3
Week 16	X_4	(X_3 +1) - ≤ X_4
Week 20	X_5	(X_4 +1) - ≤ X_5
Week 24	X_6	(X_5 +1) - ≤ X_6
Week 24/EOT	X_{Last}[c]	(Previous Feminine Product Returned Visit +1)] – ≤ X_{Last}

[a] If feminine products are collected at more than 1 visit within a given visit window (Table 2), the last feminine product collection date will be used to define the time window. If the patient missed the previous visit, a planned study visit date will be used to calculate the window.

[b] In the absence of feminine product collection due to amenorrhea the visit date when amenorrhea was reported will be used.

[c] Date of last non-missing feminine product collection within the interval from (last dose date – 35) to (last dose date + 7 days) (see Section 7.3.3).

4.4. General Rules for Missing Data

Handling of missing data for the primary efficacy analysis is described in Section 7.3.5.

4.4.1. By-Visit Endpoints

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

4.4.2. Adverse Events and Concomitant Medications

The following imputation rules for the safety analyses will be used to address the issues with partial dates. The imputed dates will be used to determine the treatment-emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end dates of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default.

The following rules will be applied to impute partial dates for adverse events:

- If start date of an adverse event is partially missing, impute as follows:
  - If both Month and Day are missing and Year = Year of treatment start date, then set to treatment start date as long as adverse event end date is not prior to treatment start date;
  - If both Month and Day are missing and Year ≠ Year of treatment start date, then set to January 1;
  - If Day is missing and Month and Year = Month and Year of treatment start date, then set to treatment start date as long as adverse event end date is not prior to treatment start date;
  - If Day is missing and Month and Year ≠ Month and Year of treatment start date, then set to first of the month;
  - If start date is completely missing, set to treatment start date as long as adverse event end date is not prior to treatment start date.
- If end date of an adverse event is partially missing, impute as follows:
  - If both Month and Day are missing, then set to December 31;
  - If only Day is missing, then set to last day of the month;
  - If end date is completely missing, do not impute.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both).

The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both Month and Day are missing, then set to January 1;

  - If only Day is missing, then set to the first of the month.
- If end date of a medication is partially missing, impute as follows:
  - If both Month and Day are missing, then set to December 31;
  - If only Day is missing, then set to last day of the month.

If start date or end date of a medication is completely missing, do not impute.

5. STUDY POPULATION

5.1. Subjects Disposition

The number of patients for each of the following categories will be summarized by treatment group:

- All randomized patients;
- Patients included in the Safety population;
- Patients who completed the 12-Week randomized treatment period;
- Patients who completed the 24-Week randomized treatment period;
- Patients who discontinued early from the 24-Week randomized treatment period and reasons for discontinuation;
- Patients who enrolled in the extension study;
- Patients who entered the Post-Treatment Follow-Up Period and did not enroll in the extension study.

Patient disposition will be summarized for all randomized patients. Summaries will include the number and percentage of patients in the mITT and Safety populations. The number and percentage of patients who prematurely discontinue study drug and the reasons for discontinuation will be summarized by treatment group. The number and percentage of patients who continue into the extension study (MVT-601-3003) will also be summarized by treatment group.

5.2. Screen Failure

Reasons for screen failure will be summarized. Number and percentage of patients who did not pass screening will be based on the patients who signed the informed consent form but were not randomized.

5.3. Protocol Deviations

Protocol deviations will be categorized as important or minor per the protocol deviation plan. Important protocol deviations will include, but will not be limited to, the following categories:

- Randomized patient who did not satisfy key entry criteria;
- Randomized patient who met withdrawal criteria during the study but was not withdrawn;
- Randomized patient who received the wrong treatment;
- Randomized patient who received a prohibited concomitant medication that met criteria for an important protocol deviation;
- Unintentional unblinding of treatment assignment.

Important protocol deviations will be summarized by deviation category for all patients in the mITT population. A patient listing of all important protocol deviations will be provided.

In addition, patient eligibility, including inclusion criteria that are not met and exclusion criteria that are met at randomization enrollment, will be summarized for all patients in the mITT population.

A selected subset of the major protocol deviations that are likely to affect analysis of efficacy will be identified to define the Per-Protocol population prior to the database lock. This subset will include but will not be limited to the following important protocol deviations:

- Did not satisfy key entry criteria **(**restricted to patients with missing Baseline MBL volume or ineligible Baseline MBL volume);
- Drug compliance < 75%;
- Patient received prohibited concomitant medications that met criteria for important protocol deviation: restricted to patients who received prohibited concomitant medications that may cause significant drug-drug interaction;
- Unintentional unblinding of treatment assignment.

5.4. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by treatment group for the mITT population. Categorical data will be summarized using frequencies and percentages, by treatment group and overall (see Table 6 below). Summaries of continuous data will display the mean, SD, median, minimum, and maximum. The numbers of missing values will also be summarized.

Table 6: Categories for Demographic and Baseline Characteristics

Variable	Category
Age (years)	< 40, ≥ 40
Geographic region	North America, Rest of World
Race	Black or African American, White, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino or Not reported
BMI (kg/m^2) at Baseline	< 18.5, 18.5 to <25, 25 to <30, 30 to < 35, 35 to < 40, ≥ 40
History of prior pregnancy	Yes, No
Disease duration of uterine fibroid (years)	Min to <1, ≥ 1 to < 3, ≥3 to <5, ≥5 to <10, ≥ 10
Type of uterine fibroids	
Subserous fibroid	Yes, No
Intramural fibroid	Yes, No
Submucosal fibroid	Yes, No
Other	Yes, No
Any surgery for uterine fibroids	Yes, No
Volume of myoma at Baseline (cm^3)	< 25, ≥ 25
Volume of uterus at Baseline (cm^3)	< 300, ≥ 300
Menstrual blood loss volume at Baseline (mL)	< 225, ≥ 225
Menstrual blood loss volume at Baseline (mL)	< 160, ≥ 160
Hemoglobin at Baseline (g/dL)	Min to < 8, ≥ 8 to <10.5, ≥ 10.5 to <12, ≥ 12
UFS-QoL Bleeding and Pelvic Discomfort Scale	0 to < 25, 25 to <50, 50 to <75, 75 to 100
Maximum NRS score for uterine fibroid-associated pain at Baseline	< 4, ≥ 4
Patient Global Assessment	
Function	No limitation at all, mild limitation, moderate limitation, quite a bit of limitation, extreme limitation
Symptoms	Not severe, mildly severe, moderately severe, very severe, extremely severe

Abbreviations: BMI = body mass index; NRS = Numerical Rating Scale; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.

5.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term (PT). Additionally, summaries of uterine fibroid–specific medical and surgical treatment history will be provided. A patient with multiple occurrences of medical history within a PT will be counted only once in that PT.

5.6. Prior Medications and Concomitant Medications

Prior medications and concomitant medications taken during the study treatment period will be summarized for all patients in the Safety population by treatment group. Medications are considered concomitant if exposure occurs during the treatment period.

The number and percentage of patients who took at least one dose of a prior medication for treatment of uterine fibroids will be summarized by treatment group and overall using the World Health Organization (WHO) Drug Dictionary and summarized according to the Anatomical Therapeutic Chemical (ATC) Classification System and generic medication name. A patient who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6. STUDY DRUG EXPOSURE AND COMPLIANCE

Patients in the Safety population will be summarized for extent of exposure and compliance to study drug by actual treatment received. Exposure to and compliance with relugolix (or relugolix placebo) and E2/NETA (or placebo) will be summarized separately and will be based on the drug accountability case report forms.

Study drug exposure summaries will include the total dosage taken in milligrams, the total number of tablets (or capsules) taken, and the treatment duration.

Study drug compliance will be summarized for the treatment period and will be calculated as follows:

(total tablets taken / total tablets expected to be taken) x 100

The total tablets taken will be calculated as:

(total tablets dispensed - total tablets returned)

The total tablets expected to be taken is calculated as the total number of tablets a patient is expected to take each day times the length of time (in days) that the patient was in the treatment period of the study. Tablets that were dispensed and not returned will be assumed to have been taken. For patients who did not return for their last scheduled visit, tablets that were dispensed and not returned will not be included in the calculation of study drug compliance. For patients who did not return for any post-Baseline visits and did not return dispensed study drug, study drug compliance will not be calculated and will be categorized as “not able to calculate” in summaries of study drug compliance.

Summary statistics of study drug compliance (eg, mean, median, etc.) will be presented, along with a categorical summary (eg, ≤ 80%, 80 to 100%, > 100%).

7. EFFICACY ANALYSES

7.1. General Considerations

Efficacy analyses will be conducted on the mITT population according to the randomized treatment assignment. Stratified analyses will incorporate the randomization stratification factors. If the group of patients at any factor level from a randomization stratification factor (eg, patients with Baseline MBL volume ≥ 225 mL) comprises < 10% of the entire mITT population, this stratification factor (eg, Baseline MBL volume) will not be used for stratified analyses. In addition, if there are < 15 patients in 1 of the 4 strata (derived from the 2 stratification factors each with 2 levels), only stratification factor of Baseline MBL volume (< 225 versus ≥225 mL) will be used in the stratified analysis for more robust strata-adjusted estimation of treatment effect. The stratification category used at the time of randomization (in the Interactive Web Recognition Service [IWRS] system) will be used for all analyses rather than data recorded on the electronic case report form (eCRF) unless otherwise specified. A sensitivity analysis of the primary endpoint will be performed if the data in the IWRS and eCRF for stratification factors differ by > 5%.

7.1.1. Analyses for Binary Data and Other Categorical Data

Binary data will be summarized by frequency counts and percentages for each treatment group.

7.1.2. Analyses for Categorical Data

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

7.1.3. Analyses for Continuous Data

Continuous variables will be summarized using descriptive statistics (eg, *n*, mean, median, SD, minimum, maximum, and first and third quartiles). For the analyses of change from Baseline, the mean at Baseline will be calculated for all patients with at least one post-Baseline value by treatment group. Additionally, the mean will also be calculated for each visit, including only the patients who are in the analysis who have data for that visit by treatment group.

7.1.4. Analyses for Time to Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method. The median, quartiles, and probabilities of an event at particular time points will be estimated by the Kaplan-Meier method.

Confidence interval for the Kaplan-Meier estimation is calculated using the exponential Greenwood formula via log-log transformation of the survival function.

The variance of the treatment difference will be calculated using the following formula:

$$V\left[\widehat{S_R}(t) - \widehat{S_L}(t)\right] = \hat{V}\left[\widehat{S_R}(t)\right] + \hat{V}[\widehat{S_L}(t)];$$

where each of the component of the variance of the Kaplan-Meier estimate will be calculated using Greenwood's formula:

$$\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2 \sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}$$

where n_i denotes the number of patients at risk at time t_i, and d_i denotes the number of events observed at time t_i.

The 95% CI of the treatment difference will be calculated using a log-log transformation of the difference in survival function, as follows:

$$[(\widehat{S_R}(t) - \widehat{S_L}(t))^{exp(1.96\,\hat{\tau}(t))}, (\widehat{S_R}(t) - \widehat{S_L}(t))^{exp(-1.96\,\hat{\tau}(t))}]$$

$$\text{where } \hat{\tau}^2(t) = \frac{\hat{V}[\widehat{S_R}(t) - \widehat{S_L}(t)]}{\{[\widehat{S_R}(t) - \widehat{S_L}(t)]\log[\widehat{S_R}(t) - \widehat{S_L}(t)]\}^2}.$$

A stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

7.2. Multiplicity Adjustment

The primary and the ranked secondary efficacy analyses will be performed at an overall alpha level of 0.05 (two-sided) comparing relugolix + E2/NETA (Group A) with placebo (Group C). A test will be deemed statistically significant if the two-sided p-value rounded to four decimal places is < 0.05. A gate-keeping testing procedure will be applied to maintain the family-wise type I error rate for the testing of primary and ranked secondary endpoints (see Section 7.4.1 for details).

Comparative statistics (p-values, 95% CIs for differences) will be provided for the treatment comparison of relugolix + E2/NETA with placebo for all other secondary efficacy endpoints. A treatment comparison of relugolix + delayed E2/NETA (Group B) with placebo will be performed only for the primary efficacy endpoint. There will be no statistical testing for treatment differences between the relugolix groups (Group A versus Group B) for any efficacy endpoints. The relugolix + E2/NETA group and relugolix + delayed E2/NETA group will be compared for the following safety endpoints: percent change from Baseline to Week 12 in BMD and incidence of vasomotor symptoms by 12 weeks (see Section 9.3.5 and Section 9.1.7, respectively). The above comparative analyses are not part of the gate-keeping testing procedure for label claims. p-values for primary and key secondary endpoints were adjusted for multiplicity. All other p-values are provided at a nominal level of 0.05.

7.3. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the proportion of women who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline in MBL volume over the last 35 days of treatment as measured by the alkaline hematin method. The primary endpoint will be referred to as responder rate and derived on the basis of the total MBL volume measured at the Week 24/EOT visit window taking into consideration the patient's compliance with return of feminine products and completion of the eDiary (see Section 7.3.2 and Section 7.3.4 for details).

7.3.1. Primary Efficacy Analysis

The following primary hypothesis for the primary efficacy endpoint will be tested:

Null hypothesis H_{01}: $\pi_R \leq \pi_P$ versus Alternative hypothesis H_{a1}: $\pi_R > \pi_P$

where π_R and π_P are the responder rates at Week 24/EOT for relugolix + E2/NETA (Group A) and placebo (Group C), respectively.

The treatment comparison between the relugolix + E2/NETA and the placebo will be analyzed using a Cochran-Mantel-Haenszel test statistic for proportions stratified by the Baseline mean MBL volume using the alkaline hematin method (< 225 mL versus ≥ 225 mL) and geographic region (North America versus Rest of World). The difference in responder rates between the relugolix + E2/NETA and placebo and its two-sided 95% CI will be estimated using stratum-adjusted Mantel-Haenszel proportions. The unadjusted responder rates and the difference in responder rates between the relugolix + E2/NETA and placebo groups and the corresponding two-sided 95% CI also will be provided. The study will be considered positive if the treatment effect for the primary endpoint is statistically significant with two-sided p-value < 0.05.

For the primary analysis, primary endpoint will incorporate the missing data handling rules described in Section 7.3.5.

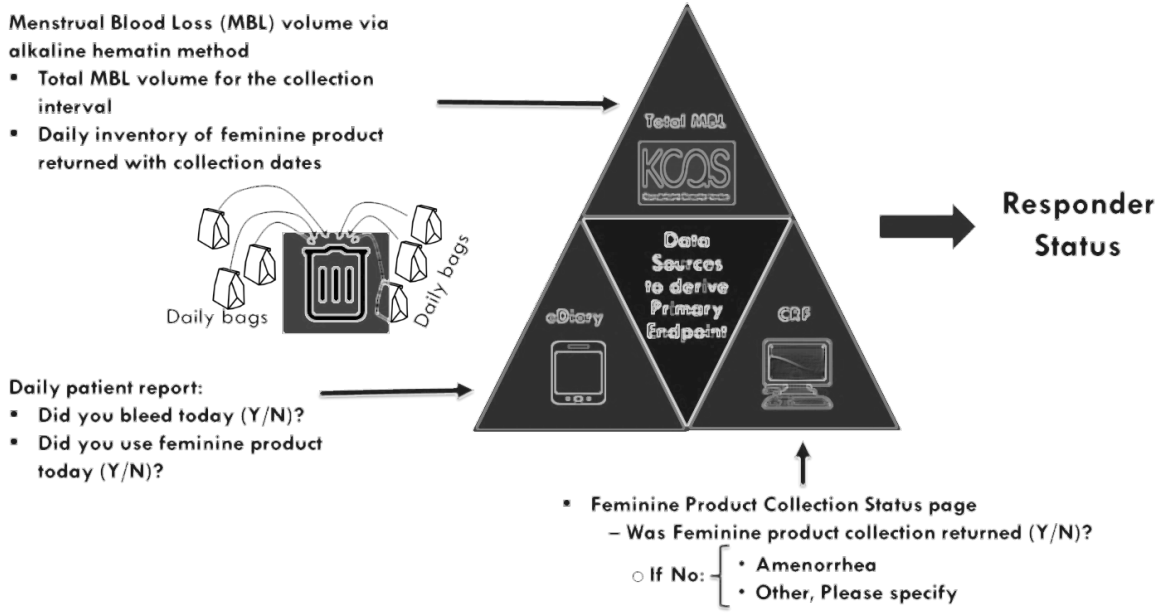
7.3.2. Data Sources Supporting Derivation of Responder Status

The data sources that will be used to support derivation of responder status, the primary endpoint, are depicted in Figure 2 below. They include:

- Menstrual blood loss volume determined by the alkaline hematin method;
- Daily patient report of bleeding (yes/no) and use of feminine product (yes/no) captured in the eDiary;
- The status of feminine product (FP) collection return (yes/no) recorded on the eCRF page at each visit with specific reasons captured when no product collection was returned.

The total MBL volume is reported from the analysis of FP returned for each collection interval. An inventory of days (with dates) for which FP was collected and returned is also available. This inventory is aligned with patients' reports of bleeding and FP use in the eDiary. The status of FP collection return, and specifically the reason for non-return of FP reported on the Feminine Product Collection eCFR page is used to support derivation of responder status (see Section 7.3.5 for details).

Figure 2: Data Sources Supporting Derivation of Primary Endpoint



Abbreviations: CRF = case report form.

7.3.3. Definitions Related to Menstrual Blood Loss

Menstrual Blood Loss Volume

All returned feminine products (validated, validated but unauthorized, or unvalidated products) collected at each visit will be analyzed by the alkaline hematin method to obtain the MBL volume. The MBL volume measured over the Week 24/EOT feminine product collection interval (up to 35 days prior to the last dose of treatment) will be used for analysis of the primary efficacy endpoint (see details below). The vendor, KCAS, reports when unauthorized feminine products (products not dispensed for use in the trial) have been returned. KCAS also reports whether the unauthorized products have previously been validated for their analysis. The report details MBL volumes for authorized, unauthorized but validated, and unauthorized and unvalidated products.

Validated Menstrual Blood Loss Volume

All returned feminine products collected at each visit, with the exception of unvalidated products, will be assessed by the alkaline hematin method to obtain the validated MBL volume. The validated MBL volume is derived from assessments of all returned validated feminine products (including validated and validated but unauthorized products) and will be used for sensitivity analysis.

Baseline Menstrual Blood Loss Volume

Baseline MBL volume is defined as the average MBL volume from the one or two consecutive screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method as follows:

For patients with MBL volume ≥ 160 mL during the screening period, the Baseline MBL volume is the last measurement collected before the first administration of study drug.

If the MBL volume is < 160 mL, the Baseline MBL volume is defined as the average of the MBL volume from the two screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method (see Figure 4-2 of the study protocol for details).

Week 24/EOT Feminine Product Collection Interval

To ensure collection of all feminine products used during that menstrual cycle, an interval of up to 35 days for measurement of the primary endpoint was selected to accommodate women who continue to have cyclic bleeding on study treatment and whose natural cycle was at the upper end of the normal cycle duration range. This method is consistent with that used during screening for collection of feminine products. Specifically, the feminine product collection interval at Week 24/EOT is driven by types of bleeding patterns experienced by the patients, as described below:

- For patients who continue to have cyclic bleeding, the length of the interval depends on the duration of the patient's natural cycle; this is consistent with the way the Baseline MBL volume was determined (eg, the interval ranging from approximately 21 to 35 days);
- Patients who report irregular, non-cyclic bleeding are instructed to collect and return all feminine product used between study visits, up to 35 days, as per the schedule of events;
- For patients who report amenorrhea on the feminine production collection eCRF page, an interval of last 35 days of treatment will be reviewed to ensure that reported amenorrhea is not due to incomplete collection.

For patients who are in the midst of an episode of cyclic bleeding at the time of the Week 24/EOT visit, the visit window may be extended up to 7 days after the last dose of study drug to ensure patients return all used feminine products over that bleeding episode.

Per protocol, all used feminine products are to be collected at each visit and returned for analysis using the alkaline hematin method. For patients who continue to have menstrual bleeding, study visits are timed such that the feminine products used in the entire menstrual bleeding cycle are collected in one container provided at each visit.

MBL Volume at Week 24/EOT

MBL volume at Week 24/EOT is defined as the MBL volume obtained from the feminine product returned over the Week 24/EOT feminine product collection interval, as described above. The MBL volume at Week 24/EOT will be used to derive the primary efficacy endpoint.

If a patient did not return feminine product over the last 35 days of treatment and reported amenorrhea on the feminine product return eCRF page, she will be considered as amenorrhoeic and her MBL volume will be assigned as 0 mL.

Feminine Product Return Rate at Week 24/EOT

To quantify degree of compliance with feminine product collection, the FPRR will be calculated based on the inventory of feminine product returned by day (dates) summarized on the Feminine Product Collection eCFR page (provided by the vendor, KCAS) and responses to the eDiary Question 4 regarding bleeding experience and Question 5 regarding the use of feminine product obtained for the corresponding eDiary window (see Table 5). Specifically:

- For those who returned feminine product at Week 24/EOT, the FPRR was calculated as the observed number of days with returned feminine products (based on the inventory of FP received by KCAS) divided by the expected number of days with bleeding and use of product as reported on the eDiary within the Week 24/EOT feminine product collection interval (as defined above).
- For those who did not return any feminine products:
  - If the reason was amenorrhea reported on the eCRF or if spotting/negligible bleeding was reported on the eCRF and confirmed by eDiary over the Week 24/EOT visit window, their FPRR will be set to 100% because the lack of menstruation obviates the need for feminine product collection.
  - Otherwise if the reason is any other, their FPRR was set to 0.

$$\text{FPRR} = \frac{\text{observed (No. of days with returned FP [per KCAS])}}{\text{expected (No. of days reported bleeding and use of FP [per eDiary])}} x100$$

Return of feminine products will be summarized in the CSR for Week 24/EOT visit.

7.3.4. Definition of Responder at Week 24/EOT

A responder at Week 24/EOT is defined as a patient who satisfies both the following:

- Had MBL volume of < 80 mL at Week 24/EOT;
- Had at least a 50% reduction from Baseline in MBL volume at Week 24/EOT.

The reduction from Baseline in MBL volume at Week 24/EOT will be calculated as the absolute change at Week 24/EOT in MBL volume from the Baseline MBL volume divided by the Baseline MBL volume.

Responder status at Week 24/EOT will be assessed based on the reported MBL volume at Week 24/EOT, in conjunction with treatment duration, compliance with feminine product collection, and compliance with eDiary entry over the same visit window (see Section 7.3.5 for details).

7.3.5. Derivation of Responder Status at Week 24/EOT and Missing Data Handling Rules

For the evaluation of primary endpoint, missing data handling rules will be implemented for deriving responder status at Week 24/EOT as described below. The following elements will be checked: duration of treatment exposure; compliance with feminine product collection against the eDiary, as measured by FPRR; compliance with eDiary entry, defined as the proportion of eDiary entry days over the length (days) of FP collection interval for Week 24/EOT visit; and reasons for no FP collection (as displayed in Table 7).

Patients with < 4 weeks of treatment who withdraw from the study prematurely due to lack of efficacy or withdraw from the study prematurely to undergo surgical intervention for uterine fibroids will be considered as non-responders.

All other patients will have their responder status determined as follows:

- For patients with a FPRR of 100%, responder status will be determined based on the observed MBL volume;
- For patients who had incomplete feminine product collection, with a FPRR of < 100%, responder status will be derived based on either imputed or observed MBL volume;
  - Those with an MBL volume ≥ 80 mL or < 50% reduction from Baseline will be considered as non-responders;
  - Those with an MBL volume < 80 mL and ≥ 50% reduction from Baseline will be imputed for partial or complete missing MBL volume (see Section 7.3.6 for details).
- For patients who did not return a feminine product collection, responder status will be determined depending on the reason reported on the Feminine Product Collection eCRF:
  - If the reason is reported as Amenorrhea, the last 35 days of treatment will be used to derive responder status:
    - If the Week 24/EOT interval was 35 days, then she will be considered as a responder;
    - If the Week 24/EOT interval was <35 days, the following supportive information will be used to derive responder status:
      - If a patient reported amenorrhea at the visit prior to Week 24/EOT, she will be defined as a responder;
      - If a patient did not report amenorrhea at the visit prior to Week 24/EOT, eDiary data from the prior visit interval will be reviewed to confirm whether the patient was amenorrheic for a total of 35 days.
        - If the eDiary from the previous interval confirms amenorrhea, then the patient will be considered as a responder;

- Otherwise, MBL volume will be imputed.

- If the reason is Other and the specification describes spotting or negligible bleeding, responder status will be defined as follows:
    - The patient will be considered as a responder if it is supported by the eDiary data: the eDiary entry rate must exceed 70% and the patient must have reported no more than 5 total days of bleeding with product use and no more than 3 consecutive bleeding with product use over the collection interval.
    - If the eDiary entries did not confirm spotting or negligible bleeding, but the patient had at least 8 weeks of MBL volume data prior to the Week 24/EOT visit, her missing MBL volume will be imputed to determine responder status. Eight weeks of MBL volume data represents a reasonable minimum length of observation to justify imputation of the remaining data in assessing the effects of hormonal therapy.
    - Otherwise if the patient had < 8 weeks of MBL volume data, she will be considered as a non-responder;
- If the reason is any Other, the responder status will be derived as follows:
    - If the patient had at least 8 weeks of MBL volume data prior to the Week 24/EOT visit, her missing MBL volume will be imputed and her responder status will be based on the imputed MBL volume.
    - If the patient had < 8 weeks of MBL volume data, she will be considered as a non-responder.

Table 7: Derivation of Responder Status at Week 24/EOT and Missing Data Handling Rules – for Primary Analysis

Treatment Exposure	FP Collection (FPRR)	Observed MBL Volume	Reason for No FP Collection	Responder Status
< 4 weeks	N/A	N/A	N/A	Imputed as non-responder
≥ 4 weeks	100% FP Compliance	N/A	N/A	Based on the observed MBL volume
	<100% FP Compliance	MBL volume ≥ 80 mL or <50% reduction from Baseline	N/A	Imputed as non-responder based on the observed MBL volume
		MBL volume < 80 mL and ≥ 50% reduction from Baseline	N/A	**Based on the imputed MBL volume**
	No FP Collection	N/A	Reported "Amenorrhea"	Imputed as responder
			Reported "Spotting or negligible bleeding" and confirmed by eDiary[a]	Imputed as responder
			Reported "Spotting or negligible bleeding" although not confirmed by eDiary or any other reason, had at least 8 weeks of MBL volume data	**Based on the imputed MBL volume**
			The entries in the eDiary did not verify "Spotting or negligible bleeding" or any other reason and if had < 8 weeks of MBL volume data	Imputed as non-responders

Abbreviations: eDiary, electronic diary; FP, feminine product; EOT, end of treatment; MBL, menstrual blood loss; N/A, not available.

[a] Defined as those patients who meet the following criteria: eDiary entry rate > 70% and no more than 3 consecutive days and no more than 5 days of bleeding/spotting and use of feminine product reported on the eDiary over the Week 24/EOT visit window (see Table 5).

7.3.6. Mixed-Effects Model for Imputing Missing or Partially Missing MBL Volume at Week 24/EOT

For the primary analysis, patients with missing MBL volumes at Week 24/EOT will be identified per missing data handling rules as described above. For imputing missing data for the primary analysis, a mixed-effects model approach will be used, as the mixed-effects approach may better describe the effects of a hormonal treatment (such as suppression of the hypothalamic-pituitary-ovarian axis by GnRH antagonists).

Specifically, a mixed-effects model with repeated measures of MBL volumes at multiple time points (Weeks 4, 8, 12, 16, 20 and 24) will be fitted to predict percent change in MBL volume from Baseline (as a dependent variable) through the fixed-effects associated with covariates (ie, stratification factors of Baseline MBL volume and geographic region, visit, treatment, and visit by treatment interaction) and random effects (from the individual patients). In this model, an unstructured variance-covariance matrix is assumed for each patient.

See sample SAS codes below for illustration where PCHG_MBL is percent change in MBL volume from Baseline as a dependent variable, PID is patient identification number, BMBL is a randomization stratification factor (Baseline MBL < 225 vs ≥ 225), REGION is a randomization stratification factor (North America vs Rest of World), TRT is treatment group (relugolix + E2/NETA or Placebo), VISIT is visit time point (4, 8, 12, 16, 20, and 24 weeks) and TRT*VISIT is the visit by treatment interaction. The specification of type=UN implements unstructured variance-covariance matrix for an individual patient with multiple measures of MBL volumes.

```
proc mixed data=MBL_dataset method=REML covtest;
class PID BMBL REGION TRT VISIT;
model PCHG_MBL= BMBL REGION VISIT TRT VISIT*TRT/s outp=ufmi_mixed_p
covb;
repeated VISIT /type=UN subject=PID r;
lsmeans TRT/diff;
ods output SolutionF=mixparms CovB=mixcovb;
```

Applying this model over the observed longitudinal MBL volume data, the fixed-effects will be estimated and relationship of percent change in MBL volume from Baseline with the covariates will be characterized by the fitted model. From the fitted model, the percent change in MBL volume (whether missing or not) will be predicted for each patient at each visit and in a particular stratum. The imputed MBL volume will be obtained by first multiplying the imputed percent change with the individual patient's Baseline MBL volume to the difference, and then adding the Baseline BML volume to the difference.

The main reason for using percent change in MBL volume over reported MBL volume as a dependent variable in the mixed-effects model is that the percent change is part of the derivation of the primary endpoint. Secondly, the percent change is a normalized value adjusted for the Baseline value and less influenced by Baseline MBL volume, and therefore it is a better metric to describe the relationship of MBL volume reduction with hormonal treatment and to impute the missing volumes in a more robust fashion.

Since the purpose of using a mixed-effects model is imputing the missing MBL volumes identified at Week 24/EOT, the predicted MBL volumes at the corresponding Week 24/EOT visit will be used to determine responder status. For patients without the need for imputation, their responder status will be derived according to the algorithms laid out in Table 7. This imputation approach is consistent with the definition of responder at Week 24/EOT for the primary analysis.

7.3.7. Sensitivity Analyses

To assess the robustness of the primary analysis, the following sensitivity analyses of the primary endpoint will be conducted at Week 24/EOT.

7.3.7.1. Sensitivity Analysis 1

To assess the potential impact of unvalidated feminine product use, the primary endpoint will be analyzed as sensitivity analysis in a similar fashion to the primary analysis using the Week 24/EOT validated MBL volume (obtained from the validated or validated-but-unauthorized feminine products only and excluding unvalidated products).

7.3.7.2. Sensitivity Analysis 2

To assess the potential impact of missing data due to inadequate collection of feminine products, the primary endpoint will be analyzed with a sensitivity analysis using the missing data handling rules as described in Table 8 below where the observed MBL volume will be used to assess the responder status at Week 24/EOT when feminine product collection was incomplete. These rules differ from those used in the primary analysis in that no imputation will be implemented for patients with < 100% feminine product compliance and the reported MBL volume both < 80 mL and a ≥ 50% reduction from Baseline as highlighted in Table 8.

Table 8: Derivation of Responder Status at Week 24/EOT and Missing Data Handling Rules – for Sensitivity Analysis

Treatment Exposure	FP Collection (FPRR)	Observed MBL Volume	Reason for No FP Collection	Responder Status
< 4 weeks	N/A	N/A	N/A	Imputed as non-responder
≥ 4 weeks	100% FP Compliance	N/A	N/A	Based on the observed MBL volume
	< 100% FP Compliance	MBL volume ≥ 80mL or < 50% reduction from Baseline	N/A	Imputed as non-responder based on the observed MBL volume
		MBL volume < 80mL and ≥ 50% reduction from Baseline	N/A	**Based on the observed MBL volume**
	No FP Collection	N/A	Reported "Amenorrhea"	Imputed as responder
			Reported "Spotting or negligible bleeding" and confirmed by eDiary[a]	Imputed as responder
			Reported "Spotting or negligible bleeding" although not confirmed by eDiary or any other reason, had at least 8 weeks of MBL volume data	Based on the imputed MBL volume
			The entries in the eDiary did not verify "Spotting or negligible bleeding" or any other reason and if had < 8 weeks of MBL volume data	Imputed as non-responders

Abbreviations: eDiary, electronic diary; FP, feminine product; EOT, end of treatment; MBL, menstrual blood loss; N/A, not available.

[a] Defined as those patients who meet the following criteria: eDiary entry rate >70% and no more than 3 consecutive days and no more than 5 days of bleeding/spotting and use of feminine product reported on the eDiary over the Week 24/EOT visit window (see Table 5).

7.3.7.3. Sensitivity Analysis 3

To assess the potential impact of early discontinuation on the primary endpoint, the primary endpoint will be analyzed with a sensitivity analysis defining the patients' responder status as follows:

- Patients who discontinued study drug during the first 4 weeks for any reason or who discontinued study drug between Week 4 and Week 12 due to an adverse event, surgery or other intervention for heavy menstrual bleeding, reported lack of efficacy, or bleeding complaints will be considered as non-responders;
- All other patients will have their responder status defined using data from the Week 24/EOT assessment period using the last observation carried forward method.

7.3.7.4. Sensitivity Analysis 4

To assess the potential impact of the length and full exposure of the treatment, the primary endpoint will be analyzed for the Completers population as a sensitivity analysis. The Completers population is defined as patients in the mITT population who completed 24 weeks of study treatment.

7.3.7.5. Sensitivity Analysis 5

The primary endpoint will be analyzed on the Per-Protocol population as a sensitivity analysis, using the methods specified for the primary analysis (see definition of Per-Protocol population in Section 4.2.2).

7.3.7.6. Sensitivity Analysis 6

As a sensitivity analysis to the primary analysis using the mixed-effects model for imputing missing MBL volumes at Week 24/EOT, multiple imputation approach will be implemented as described below.

A multiple imputation method (Rubin, 1987; von Hippel, 2018) will be used to impute missing or partially missing MBL volume identified by the missing data handling rules (see Table 7 and Table 8) at Week 24/EOT as described in the following 5 steps. In this method, an arbitrary missing pattern will be assumed using Markov Chain Monte Carlo imputation to generate a monotone missing pattern for the observed longitudinal MBL volume values (including 0 mL if the patient has amenorrhea). Imputation will be performed separately by randomized treatment group (Sullivan, 2018), given the distinct bleeding patterns among the three treatment groups.

Normalizing transformations will be applied to the statistics estimated from each imputed dataset before the Rubin's combination rules can be applied (Ratitch, 2013). This combined estimation and statistical test will account for the additional variability due to imputation to provide a robust assessment of the treatment effect.

Step 1: Identifying patients with missing or incomplete MBL volume from the longitudinal MBL volume dataset as collected.

Step 2: Generating a monotone missing pattern using the Markov Chain Monte Carlo technique by imputing missing MBL volume measurements that are between non-missing results.

Step 3: Imputing the remaining missing values m = 100 times using a regression model; therefore, generating 100 complete longitudinal MBL volume datasets.

Note: if a patient missed Week 8 and prematurely discontinued study drug (eg, at Week 20) and MBL volume at Week 20 is missing or partially missing, MBL volume will be imputed for intermittent missing data at Week 8, Week 20 (EOT), and Week 24 due to discontinuation.

Step 4: Performing the same CMH test pre-specified for the primary endpoint analysis and estimating the responder rates for each arm using each of the 100 datasets based upon the MBL volume at Week 24/EOT.

Note: in the example above, the imputed MBL volume at Week 20 (EOT) will be used in the analysis, although MBL volume is imputed at Week 24.

Step 5: Combining the results from the 100 complete datasets to make inferences about the treatment effect on the responder rate.

7.3.8. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint comparing the relugolix + E2/NETA group versus the placebo group will be performed to assess whether treatment effects are consistent across clinically important subgroups. The odds ratio and its 95% CI based on a logistic regression model will be displayed in a forest plot for each subgroup. The logistic regression model will include treatment group, Baseline MBL volume value and geographic region as covariates. Subgroups will include, but will not be limited to, the subgroups outlined in Table 9.

Table 9: Planned Subgroup Analyses

Subgroup Name	Subgroup Level
Geographic region	North America vs Rest of World
Menstrual blood loss volume at Baseline (mL)	< 225 vs ≥ 225 < 120, 120 to < 160, 160 to < 225, ≥ 225
Age category (years)	< 40 vs ≥ 40 < 35, 35 to < 40, 40 to < 45, ≥ 45
Race	Black or African American vs Not Black or African American; Black or African American, White, Other
Volume of myoma at Baseline (cm^3)	< 25 vs ≥ 25
Volume of uterus at Baseline (cm^3)	< 300 vs ≥ 300
BMI (kg/m^2) at Baseline	< 30 vs ≥ 30 < 25, 25 to < 30, 30 to < 35, 35 to <40, ≥ 40
Maximum NRS score for uterine fibroid–associated pain at Baseline	< 4 vs ≥ 4
History of prior pregnancy	Yes/No

Abbreviations: BMI = body mass index; NRS = Numerical Rating Scale.

7.4. Secondary Efficacy Endpoints

Secondary efficacy variables include seven key secondary endpoints with alpha-protection and other secondary endpoints. All secondary efficacy endpoints and analyses are summarized in Appendix 1.

The treatment effect of relugolix + E2/NETA (Group A) compared to placebo (Group C) will be tested for the alpha-protected secondary endpoints using a gate-keeping procedure (see Section 7.4.1).

Comparative statistics (p-values, 95% CIs for differences) will be provided for treatment comparison of the relugolix + E2/NETA group with the placebo group for all other secondary efficacy endpoints. Treatment difference between the relugolix + delayed E2/NETA group and the placebo group will be formally tested only for the primary efficacy endpoint. There will be no statistical testing for treatment differences between the relugolix groups (relugolix + E2/NETA group against relugolix + delayed E2/NETA group) for any efficacy endpoint (see Section 7.4.2).

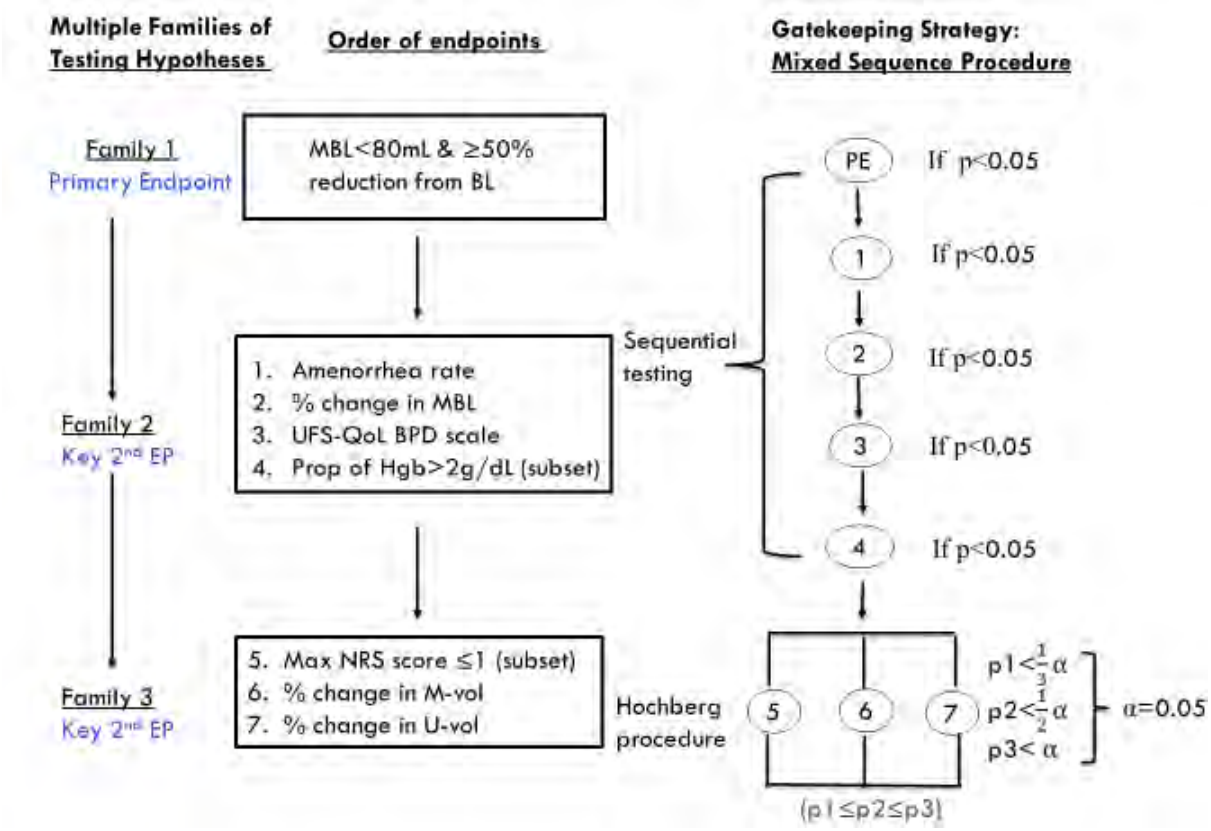
7.4.1. Key Secondary Efficacy Endpoints with Alpha-Protection

For testing whether relugolix + E2/NETA (Group A) is statistically significantly superior to placebo (Group C) for the primary efficacy endpoint as well as the seven key secondary endpoints listed below, a gate-keeping mixed sequence testing procedure will be applied to maintain the family-wise type I error rate. Under this testing procedure, the primary endpoint

will be tested first at a 2-sided 0.05 significance level. If the p-value for primary endpoint is < 0.05, the seven key endpoints listed below will be tested sequentially in the order depicted in Figure 3.

For the relugolix + E2/NETA group to be considered statistically superior to the placebo group on a secondary endpoint, the two-sided p-value must be < 0.05 for that secondary endpoint and for all higher-ranking secondary endpoints, as well as for the primary endpoint. If the two-sided p-value is < 0.05 for the fourth endpoint (proportion of women with a hemoglobin ≤ 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24), the remaining three endpoints (the fifth, sixth, or seventh) will be tested using the Hochberg step-up procedure.

Figure 3: Mixed Sequence Testing Procedure for Primary and Key Secondary Endpoints



Abbreviations: BPD = Bleeding and Pelvic Discomfort; EP = endpoint; Hgb = hemoglobin; max = maximum; MBL = menstrual blood loss; M-vol = myoma volume; NRS = Numerical Rating Scale; PE = primary endpoint; Prop = proportion; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort; U-vol = uterine volume.

From the Hochberg procedure, the p-values will be calculated for the three endpoints (5, 6, and 7) and ranked from the smallest to the largest. The endpoint corresponding to the largest p-value gets tested first. If the p-value is < 0.05, then no further testing will occur, and it will be concluded that all three endpoints are positive. Otherwise, the endpoint corresponding to the second largest p-value will be tested. If the p-value is < 0.025, then no further testing will occur, and it will be concluded that the endpoints corresponding to the middle and smallest p-values are positive. Otherwise, the endpoint with the smallest p-value will be tested. If the p-value is < 0.0167, no further testing will occur, and it will be concluded that only the endpoint with the smallest p-value is positive. Otherwise, all three endpoints did not pass the statistical significance criterion at 0.05 level.

The seven key secondary efficacy endpoints are as follows:

1. Proportion of women who achieve amenorrhea over the last 35 days of treatment;
2. Percent change from Baseline to Week 24 in MBL volume;
3. *Change from Baseline to Week 24 in Bleeding and Pelvic Discomfort Scale score as measured by the UFS-QoL Symptom Severity Scale (Q1, Q2, Q5);*
4. *Proportion of women with a hemoglobin ≤ 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24*
5. *Proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;*
6. Percent change from Baseline to Week 24 in uterine fibroid volume;
7. Percent change from Baseline to Week 24 in uterine volume.

For key secondary efficacy endpoints (1, 4, and 5) that are evaluating proportions, treatment comparisons will be performed using a stratified Cochran-Mantel-Haenszel test with the randomization stratification factors as strata. Point estimates and 2-sided 95% CIs for treatment differences in proportions will be provided.

For key secondary endpoint 4, an increase in hemoglobin of 2g/dL is considered clinically meaningful, because it corresponds to approximately the same increase as that expected after a transfusion of ~ 2 units of packed red blood cells (Man, 2016; Bachowski, 2017).

For deriving the key secondary endpoint 5 (proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid-associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization), the patient subset and Week 24/EOT maximum value are determined as follows.

Because patients were asked to begin eDiary entries after returning the first collection of feminine products, the number of eDiary entries made during screening varies with the duration of screening for each patient. Some patients required only one collection to be randomized, whereas others required as many as four collections to confirm eligibility.

Once the qualifying menstruation was completed and the patient qualified for randomization based upon resulting MBL volume(s), the recording of patient's NRS scores for screening phase

will be ended and the number of pain score days at Baseline can be as short as 7 days or as long as 70 days prior to randomization. If a patient meets the subset definition (maximum NRS score ≥ 4 at Baseline) over a portion of the screening days (eg, 7-70 days), she will also meet the subset definition on the entire 35 days interval.

Since the maximum NRS value is used to determine inclusion into the subset rather than an average NRS value, the variable number of days for inclusion of patients has no major impact on determining patient subset. To ensure robust estimate of response, the minimum number of non-missing daily pain scores required to calculate the maximum score at Week 24/EOT is at least 28 days (80% of the last 35 days of treatment) of pain scores recorded in the e-Diary entry.

The primary analysis of key secondary endpoint 5 will be analyzed for the subset of women who have a maximum pain score ≥ 4 during the 35 days prior to randomization and who have at least 28 days (80% of the last 35 days of treatment) of pain scores recorded in the e-Diary at Week 24/EOT. In addition, a sensitivity analysis will be conducted on the subset of women who have a maximum pain score ≥ 4 during the 35 days prior to randomization without restricting number of days of pain scores recorded in the e-Diary.

The analysis for endpoint 5 (proportion of women who achieve a maximum NRS score ≤ 1 for uterine fibroid-associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization) will also be performed using NRS scores reported on eDiary during menstrual and non-menstrual days.

For key secondary efficacy endpoints (6 and 7) evaluating percent change from Baseline in uterine fibroid volume and uterine volume that are measured only at Week 24, an analysis of covariance (ANCOVA) model will be used to assess treatment effect with treatment, randomization stratification factors and Baseline value as covariates.

For key secondary efficacy endpoints (2 and 3) evaluating the change (absolute or % change) from Baseline to Week 24, treatment comparisons will be performed using a mixed model repeated measures approach with treatment, visit, randomization stratification factors and treatment by visit interactions included as fixed effects and random effects (from the individual patients). In this model, an unstructured variance-covariance matrix is assumed for each patient.

7.4.2. Other Secondary Efficacy and Exploratory Endpoints

The following describes the analysis methods for other secondary efficacy endpoints and exploratory endpoints. There are three types of analyses corresponding to the three types of endpoints (time-to-event, continuous and binary) (see Appendix 1 for details).

Time-to-Event Endpoint

For time to achieving an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume (as an event), time to event will be defined as weeks from date of first dose of study drug to response (event) based on the MBL volume as assessed by the alkaline hematin method. The missing data handling rules described in Section 7.3.5 for deriving responder status at Week 24/EOT will be applied similarly at Weeks 8, 12, 16, and 20. Patients without an event will be censored at the last assessment date prior to the last dose of the study drug. Kaplan-Meier methods will be used to describe the time to event distributions. A log-rank test stratified by the randomization stratification factors using the proportional hazard model (p-value

from score test) will be used to compare relugolix + E2/NETA to placebo. Randomization stratification factors will be used to stratify inferential testing.

Continuous Endpoints

For endpoints evaluating the change (absolute or percent change) from Baseline to Week 24, treatment comparisons will be performed using a mixed model repeated measures approach with treatment, randomization stratification factors, visit, and treatment by visit interactions included as fixed effects. The Baseline value will be included as a covariate, and an unstructured variance-covariance matrix will be assumed. Calculation of the dependent variable (change from Baseline) for each patient at each visit will be calculated based on the visit windows specified in Section 4.3.5. Based on this model, the least squares mean at Week 24 will be compared between treatment groups and summarized along with the corresponding 95% CIs for treatment difference. In addition, summary statistics (mean change or mean % change) will be graphically presented as appropriate.

Binary Endpoints

For endpoints evaluating proportions, treatment comparisons will be performed using a stratified Cochran-Mantel-Haenszel test as appropriate with the randomization stratification factors as strata. Point estimates and 2-sided 95% CIs for treatment differences in proportions will be provided.

Descriptive statistics (point estimates and corresponding 95% CIs) will be provided by treatment group and visit as appropriate for all secondary endpoints.

Responder rate by visit (at Week 4, Week 8, Week 12, Week 16, and Week 20) will be derived in a similar fashion to the derivation of responder rate at Week 24/EOT. The missing data handling rules described in Section 7.3.5 for deriving responder status at Week 24/EOT will be applied similarly at Weeks 4, 8, 12, 16, and 20.

7.4.3. Derivation of Amenorrhea-Related Endpoints

Determination of Amenorrhea

Rules for determining amenorrhea in the treatment period is defined as those who meet 1 of the following requirements for 2 consecutive visits (approximately 56 consecutive days). Patients will be deemed to have amenorrhea during a visit window according to the following rules:

- No feminine product returned due to reported amenorrhea in 2 consecutive visits

OR

- No feminine product returned due to other reasons or feminine product collection with a negligible observed MBL volume coupled with other data indicating infrequent non-cyclic bleeding/spotting as described in Table 10.

Missing responses for menstrual bleeding questions in the eDiary will be treated as “No Bleeding” if eDiary compliance rate is > 70%.

Table 10: Rules for Determining Amenorrhea by Visit

Feminine Product Collection (KCAS) [a]	Supporting Data	
	Menstruation Status eCRF	**eDiary**
No feminine product collection due to reported amenorrhea	No menses start/stop dates reported	N/A
No feminine product collection due to other reasons	Per instructions for non-cyclic bleeding patterns, menses start date is reported but no menses stop date reported	• Data indicating infrequent, non-cyclic bleeding/spotting defined as bleeding/spotting with feminine product use for no more than 3 consecutive days and no more than 5 days bleeding total per visit window • eDiary entry rate > 70%
Feminine product collection with negligible observed MBL volume defined as <5 mL	Full or partial menses start and stop dates	• Data indicating infrequent, non-cyclic bleeding/spotting defined as bleeding/spotting with feminine product use for no more than 3 consecutive days and no more than 5 days bleeding total per visit window • eDiary entry rate > 70%

Abbreviations: eCRF, electronic case report form; eDiary, electronic diary; MBL, menstrual blood loss; N/A = not applicable.

[a] There is no requirement for feminine product return rate, as the determination of amenorrhea is based on the eDiary response.

Amenorrhea During the Last 35 Days of Treatment

Patients with amenorrhea over the last 35 days of treatment are defined as those who meet the definition of amenorrhea. A patient's amenorrhea status will also be summarized at Weeks 8, 12, 16, and 20. If a patient does not return for her Week 24/EOT visit, the eDiary responses for the last 35 days of treatment will be evaluated. If the criteria for infrequent, non-cyclic bleeding or spotting as indicated in Table 10 is met and the criteria for amenorrhea is met at the prior visit, the patient will be categorized as amenorrheic at Week 24/EOT. At all other timepoints, patients who do not return for a specific visit will be assigned as not amenorrheic at that visit.

Time to Amenorrhea

Time to amenorrhea is defined as the weeks from date of first dose of study drug to the start date of the amenorrhea window. Time to sustained amenorrhea will also be estimated and plotted using the Kaplan-Meier method.

The start date of amenorrhea is defined as the last feminine product collection date prior to start of amenorrhea. For example, if a patient's feminine product was collected at her Week 4 visit

and MBL volume for this cycle did not indicate amenorrhea, and the patient reported amenorrhea on Week 8 and 12 visits, then time to start amenorrhea will be defined as starting on the date of feminine product collection for Week 4. Patients who are determined to have amenorrhea at Week 4 and Week 8 will use their Week 4 feminine product collection date as start date of amenorrhea. Patients without an event will be censored at the last assessment date prior to the last dose of the study drug.

Sustained Amenorrhea Rate by Visit

A patient's sustained amenorrhea status will be summarized at Weeks 8, 12, 16, 20, and 24, based on her time to achieving and maintaining amenorrhea until the date of last study drug dose as shown in Table 11. For example, at Week 8, a patient is considered to have achieved sustained amenorrhea status if her amenorrhea started before Week 8 and was observed every visit thereafter until the last dose of the study treatment. The proportion of patients with sustained amenorrhea will be summarized by visit. If a patient met the criteria for sustained amenorrhea but discontinues from the study, this subject's amenorrhea status will be carried forward to the Week 24 visit.

Table 11: Sustained Amenorrhea Rate by Visit

	Amenorrhea Window	
Time Point	Start	End
Week 8	Determined amenorrhea at Week 4	Amenorrhea observed at Week 8 and was observed at every visit thereafter until and including the last dose of study treatment
Week 12	Determined amenorrhea at Week 8	Amenorrhea observed at Week 12 and was observed at every visit thereafter until and including the last dose of study treatment
Week 16	Determined amenorrhea at Week 12	Amenorrhea observed at Week 16 and was observed at every visit thereafter until and including the last dose of study treatment
Week 20	Determined amenorrhea at Week 16	Amenorrhea observed at Week 20 and was observed at every visit thereafter until and including the last dose of study treatment
Week 24	Determined amenorrhea at Week 20	Amenorrhea observed at Week 24

7.4.4. Derivation of Patient-Reported Outcome

7.4.4.1. Numerical Rating Scale Score for Pain Associated with Uterine Fibroids

Patients completed daily eDiaries including assessment of uterine fibroid-associated pain by the Numerical Rating Scale (NRS). Patients rated their worst pain in the last 24 hours caused by their uterine fibroids on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The maximum NRS score for pain at Week 24/EOT is calculated as the maximum NRS score during the last 35 days on study treatment. If any NRS scores for pain during the last 35 days on study treatment are missing, the maximum score will be calculated as the maximum of all non-missing scores. Baseline NRS score for uterine fibroid-associated pain is defined as the maximum NRS score from the 35 days of data collected prior to randomization.

Proportion of women who achieve a *maximum* NRS score for pain associated with uterine fibroids over the last 35 days of treatment that is at least a 30% reduction from Baseline will be summarized in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization (subset). In addition, for the subset, mean maximum NRS scores will be provided by treatment and visit. Maximum NRS score for each patient at a visit is defined as the highest NRS score reported in the visit window specified in Table 2.

7.4.4.2. UFS-QoL Score

Calculation of UFS-QoL Symptom Severity Scale Score

To calculate the Symptom Severity Scale score, a summed score is created for the items listed below and then the formula below the table is used to transform raw scores to a normalized score with a range of possible values from 0 to 100. This provides Symptom Severity Scale scores, where higher scores are indicative of greater symptom severity and lower scores indicate lower symptom severity.

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Symptom Severity	Sum 1 – 8	8, 40	32

Formula for Transformation of Symptom Severity Raw Scores ONLY:

Transformed Score = [(Actual raw score – lowest possible raw score)/(Possible raw score range)] * 100

Calculation of UFS-QoL Bleeding and Pelvic Discomfort Scale Score

The UFS-QoL Bleeding and Pelvic Discomfort (BPD) Scale has been derived from the UFS-QoL Symptoms Scale; the derivation and validation of this new scale can be found in Appendix 3. The new scale consists of the following three symptoms proximal to uterine fibroids:

- Heavy bleeding during your menstrual period (Q1)
- Passing blood clots during your menstrual period (Q2)
- Feeling tightness or pressure in your pelvic area (Q5)

To calculate the score for the BPD Scale, a summed score of the items listed below is created and then the formula below the table is used to transform the raw score to a normalized score. This provides BPD Scale scores, where higher score values are indicative of greater symptom severity and lower scores will indicate minimal symptom severity (high scores = bad).

Sub-Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Q1, Q2 and Q5	Sum 1,2,5	3, 15	12

Formula for Transformation of BPD Raw Scores ONLY:

Transformed Score = [(Actual raw score – lowest possible raw score)/(Possible raw score range)] * 100

On the basis of transformed score for BPD Scale, change from Baseline in the transformed score for BPD Scale at Week 24 will be defined as an alpha-protected key secondary endpoint comparing the relugolix + E2/NETA group with the placebo group. The proportion of patients who are responders (defined as meeting a meaningful change threshold from Baseline in the BPD Scale) at Week 24 on the transformed score for the BPD Scale will be compared between the two treatment arms (the relugolix + E2/NETA group with the placebo group) using a stratified Cochran-Mantel-Haenszel test, as appropriate. The proposed responder threshold is a 20-point change. Details in the determination of the meaningful change in the BPD Scale can be found in Appendix 4.

As a descriptive assessment on robustness of the responder analysis, a plot of the cumulative distribution function (CDF) will be provided for each treatment group to display the change from Baseline to Week 24 in the transformed score for BPD Scale on the x-axis and cumulative percentage of patients experiencing up to that change on the y-axis.

Calculation of Other UFS-QoL Scale Scores and UFS-QoL Total Score

For the other UFS-QoL scales (concern, activities, revised activities, energy/mood, control, self-conscious, and sexual function), a summed score of the items listed below is created for each individual scale. To calculate the UFS-QoL total score, the values for each individual scale are summed. Using the formula below the table, all raw scores are transformed to normalized scores. Higher scores are indicative of better health-related quality of life (high = good).

For endpoints evaluating a single question, the raw score is used in the analysis. The activity and revised activity domain scores will be summarized by treatment group.

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Concern	9+15+22+28+32	5, 25	20
Activities	10+11+13+19+20+27+29	7, 35	28
Revised activities	11+13+19+20+27	5,25	20
Energy/mood	12+17+23+24+25+31+35	7, 35	28
Control	14+16+26+30+34	5, 25	20
Self-conscious	18+21+33	3, 15	12
Sexual function	36+37	2, 10	8
HRQL TOTAL	Sum of 6 Subscale Scores[a]	29, 145	116

Abbreviations: HRQL, health-related quality of life.

[a] HRQL Total includes following scales: concern, activities, energy/mood, control, self-conscious, and sexual function.

Formula for Transformation of Raw Scores of Other Scale Scores ONLY:

Transformed Score = [(Highest possible score – Actual raw score)/(Possible raw score range)] * 100

For revised activities, the proportion of patients who are responders (defined as meeting a meaningful change from Baseline in the revised activity score) at Week 24 will be analyzed similarly to that for the change in BPD Scale score between the two treatment arms (relugolix + E2/NETA and placebo). The proposed responder threshold is a 20-point increase. Details of the determination of the meaningful change in the Revised Activities Scale score can be found in Appendix 5.

Missing Items

For any scale analyses, if < 50% of the scale items are missing, the scale should be retained using the mean scale score of the items present. If ≥ 50% of the items are missing, no scale score should be calculated; the subscale score will be considered missing.

7.4.4.3. Patient Global Assessment

The PGA for function and symptoms will be evaluated using a 5-point response scale (eg, absent, mild, moderate, severe, and very severe). To calculate change from Baseline to Week 24, the following numerical scores will be assigned to each response level:

Response Scale (Function)	Response Scale (Symptoms)	Numerical Score
No limitation at all	Not severe	1
Mild limitation	Mildly severe	2
Moderate limitation	Moderately severe	3
Quite a bit of limitation	Very severe	4
Extreme limitation	Extremely severe	5

For each item, the count and proportion of improvement by level or at least one level will be tabulated by treatment group and by visit. The denominator for the proportion will be based on the number of patients who provided non-missing responses to the items.

7.4.4.4. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire items 3 and 4 will be evaluated using the 5-point response scales (Not at all, Slightly, Moderately, Quite a bit, and Extremely) to assess level of improvement from Baseline to Week 24.

For each item, the count and proportion of improvement by level will be tabulated by treatment group and by visit. The denominator for the proportion will be based on the number of patients who provided non-missing responses to the items.

7.5. Exploratory Efficacy Endpoints

The following exploratory endpoints will be assessed for both comparisons the relugolix + E2/NETA group with the placebo group and the relugolix + delayed E2/NETA group with the placebo group:

- Change from Baseline to Week 24 in the EQ-5D-5L Scale score
- Change from Baseline to Week 24 in EQ-5D-5L visual analogue score.

7.5.1. Exploratory Efficacy Analyses

Analysis methods previously described for primary and secondary efficacy endpoint analyses will be used for the analysis of these endpoints.

8. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Plasma relugolix, plasma NET, and serum E2 trough concentrations will be listed and summarized by study, treatment group (Group A, B, or C), and visit.

Serum pharmacodynamic data (LH, FSH, E2, and progesterone) will be listed and summarized using descriptive statistics (including raw and change from Baseline) by study, treatment group (Group A, B, or C), and visit.

For pharmacodynamic assessment, the number and percentage of patients with individual E2 concentration values < 10 pg/mL, 10 to < 20 pg/mL, 20 to < 50 pg/mL, and ≥ 50 pg/mL and individual progesterone concentration values < 1 ng/mL, 1 to 5 ng/mL, and ≥ 5 ng/mL will be summarized by treatment group (Group A, B, or C) and visit.

Scatter plots with LOESS smoothing lines for MVT-601-3001 and MVT-601-3002 separately will be used to examine the relationship between mean plasma relugolix trough concentration at the given time point (collected between 18 and 30 hours after the previous dose) and the following pharmacodynamic concentrations:

- Week 12 serum LH, FSH, E2, and progesterone (separately for Groups A and B);
- Week 24 serum LH, FSH, E2, and progesterone (separately for Groups A and B, and Groups A and B combined).

In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes. The analysis plan for population PK and exposure-response analyses will be specified in a separate document.

9. SAFETY ANALYSES

Unless otherwise specified, safety analyses will be conducted using the safety population according to the treatment received by the patients.

9.1. Adverse Events

Adverse events will be collected from the time of the first dose of study drug through the safety follow up visit approximately 30 days after the last dose of study drug (the end of treatment period), or the date of initiation of another investigational agent or hormonal therapy or surgical intervention or entering extension study, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to study drug.

The severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term and system organ class using MedDRA 22.0 or higher.

A treatment-emergent adverse event is defined as any adverse event that occurs after administration of the first dose of study drug.

Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. Adverse events occurring prior to administration of any study drug will be listed and flagged in by-patient listings.

The following tabular summaries that include the number and percentage of patients will be provided:

- Overview of adverse events;
- All adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;
  - Study drug-related per investigator by SOC and PT;
  - By time to onset, SOC and PT;
- Grade 3 or above adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - Study drug-related per investigator by SOC and PT;
- Grade 2 or above adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;

  - Study drug-related per investigator by SOC and PT;
- Adverse events leading to study drug withdrawal;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Adverse events leading to dose interruption;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Adverse events resulting in fatal outcome;
  - By decreasing frequency of PT;
- Serious adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;
  - By SOC, PT, and relationship to study drug;
- Adverse events of clinical interest (ALT or AST ≥ 3 x ULN);
  - By SOC, PT, and maximum severity;
  - By decreasing frequency of PT.

Additionally, adverse event categories defined in Table 12 will be summarized by decreasing frequency of PT.

9.1.1. Relationship to Study Drug

Adverse events will be classified as "related" to study treatment if the relationship was rated by the investigator as possibly related or probably related. Adverse events related to any study drug (relugolix or placebo and E2/NETA or placebo) will be considered as related to study drug.

9.1.2. Severity of Adverse Event

Grade 2 or above adverse events will be summarized by SOC, PT, and/or maximum severity, relationship to study treatment.

9.1.3. Serious Adverse Event

Serious adverse events will be summarized by SOC, PT, and/or maximum severity, relationship to study treatment.

The data handling conventions for and the definition of a serious adverse event are discussed in this section. All deaths during the study, including the post treatment follow-up period, and deaths that resulted from a process that began during the study, should be included in the

analysis. For more details, deaths occurring during the following time periods or under the following conditions should be considered:

- Deaths occurring during participation in any study, or during any other period of drug exposure
- Deaths occurring after a patient leaves a study, or otherwise discontinues study drug, whether or not the patient completes the study to the nominal endpoint, if the death:
  - Is the result of a process initiated during the study or other drug exposure, regardless of when it actually occurs; or
  - Occurs within a time period that might reflect drug toxicity for a patient leaving a study or otherwise discontinuing drug. For drugs with prompt action and relatively short elimination half-lives, 4 weeks is a reasonable time period. For drugs with particularly long elimination half-lives or drug classes with recognized potential to cause late occurring effects, deaths occurring at longer times after drug discontinuation should be evaluated.

9.1.4. Adverse Event Leading to Withdrawal of Study Drug

Adverse events leading to withdrawal of study drug are those adverse events collected from the adverse event CRF pages with “drug withdrawn” as the action taken with study drug.

Adverse events with “drug withdrawn” as action taken due to any one of the components of study drug will be considered as leading to withdrawal of study drug.

9.1.5. Adverse Events Leading to Dose Interruption

Adverse events leading to dose interruption are those adverse events collected from the adverse event CRF pages with “drug interrupted” as their action taken with study drug.

Adverse events with “drug interrupted” as action taken due to any one of the components of study drug will be considered as leading to dose interruption.

9.1.6. Adverse Events Resulting to Fatal Outcome

Adverse events resulting in a fatal outcome are those adverse events collected from the adverse event pages with “fatal” as their outcome.

The fatal events, if any, will be provided in a by-subject listing.

9.1.7. Adverse Event Categories

In addition, adverse event categories defined in Table 12 will be summarized by decreasing frequency of PT under each safety population. Incidence of vasomotor symptoms by 12 weeks will be compared between relugolix Group A and relugolix Group B. Comparative statistics (such as p-values, 95% CIs, risk ratio) will be provided. Vasomotor symptoms throughout the studies will be summarized by SOC, PT, and maximum severity.

Table 12: Constitution of Adverse Event Categories

Category	Search Criteria
Bone health events	Osteoporosis/Osteopenia SMQ (broad) Fracture (custom SMQ): All preferred terms including the term "fracture," excluding "Tooth fracture" and "Fracture of penis"
Hepatic disorders	Drug-related hepatic disorders – comprehensive SMQ (narrow)
Metabolic disorders	Dyslipidemia SMQ (broad) Hyperglycemia/new onset diabetes mellitus SMQ (narrow)
Vasomotor symptoms	The following 5 preferred terms will be included: Hyperhidrosis; Feeling hot; Hot flush; Night sweats; Flushing
Mood disorders	MedDRA Depression and Suicide/Self-Injury SMQ (broad)

Abbreviations: HLT, High-Level Term; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardised MedDRA Query.

9.2. Laboratory Data

Laboratory parameters, including chemistry and hematology panels, specified as per protocol, and collected from the central laboratory will be tabulated and presented in by-patient listings. Urinalysis and hepatitis virus serological test results will be provided in by-patient listing only.

The National Cancer Institute CTCAE Grading Scale with numeric component will be used to categorize toxicity grade for laboratory parameters (CTCAE v5.0, dated 17 Nov 2017). Parameters that have criteria available for both low and high values (eg, hypercalcemia for a high value of calcium and hypocalcemia for a low value of calcium) will be summarized for both criteria (low and high). Patients will only be counted once for each criterion. The same patient can be counted for both criteria if she has laboratory values meeting each criterion. Shift tables will be provided for each gradable parameter to summarize Baseline toxicity grade versus worst post-Baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the Baseline versus worst post-Baseline results.

Boxplots of laboratory values over time will be plotted for key laboratory parameters. These laboratory parameters include, but are not limited to, hematology (hemoglobin, platelets, leukocytes, neutrophils), creatinine, glomerular filtration rate, and hepatic function panel (alanine

aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin).

The change from Baseline to each post-Baseline study visit will be presented by treatment group for each laboratory test in both tables and figures.

The number and proportion of patients with liver test elevations will be presented by treatment group. Liver test elevations are assessed by using post-Baseline results for ALT, AST, ALP, and total bilirubin based on the definitions presented in Table 13.

Table 13: Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN - < 3xULN ALT or AST ≥ 3x to < 5x ULN ALT or AST ≥ 5x to < 8x ULN ALT or AST ≥ 8x to < 10x ULN ALT or AST ≥ 10 to < 20x ULN ALT or AST ≥ 20x ULN
Total bilirubin	Total bilirubin > 2 × ULN
ALT or AST and total bilirubin	ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	ALT or AST ≥ 3 x ULN + total bilirubin > 2 × ULN + ALP < 2 × ULN

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

The number and percentage of patients with concurrent (defined as measurements on the same day) ALT or AST ≥ 3 times ULN and total bilirubin > 2 times ULN will also be presented.

9.3. Other Safety Analyses

9.3.1. Electrocardiograms

ECG interval results and changes from Baseline will be summarized descriptively for each scheduled visit in both tables and figures using data provided by and read by central reading.

A categorical analysis of corrected QT interval using Fridericia's calculation (QTcF) intervals will also be performed for each scheduled visit and for the maximum post-Baseline value. The number and percentage of patients in each QTcF interval category (< 450 msec, 450 to 480 msec, 481 to 500 msec, and > 500 msec) will be summarized. Categories of changes from Baseline (≥ 30 msec and ≥ 60 msec) will be summarized as well.

ECG intervals will be presented in by-patient listing. Overall ECG assessments performed by local reading will also be listed.

9.3.2. Visual Acuity

Visual Acuity Score at Baseline and at each scheduled post-Baseline assessment time point will be presented in a by-patient listing.

9.3.3. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and BMI will be summarized at Baseline and each subsequent scheduled assessment by treatment group. Change from Baseline will be calculated and presented for each parameter at all scheduled post-Baseline assessment time points in both tables and figures. All vital sign data will also be provided in by-patient listings.

Potentially clinically significant abnormalities in vital signs are defined in Table 14, and they will be summarized by using post-Baseline values that meet the defined criteria. Potentially clinically significant abnormalities will also be flagged in by-patient listings.

Table 14: Categories of Potentially Clinically Significant Abnormalities in Vital Signs

Parameter	Category
Systolic blood pressure	≥ 140 mmHg ≥ 180 mmHg
	≤ 90 mmHg
	Increase of ≥ 20 mmHg from Baseline Decrease of ≥ 20 mmHg from Baseline
Diastolic blood pressure	≥ 90 mmHg ≥ 105 mmHg
	≤ 50 mmHg
	Increase of ≥ 15 mmHg from Baseline Decrease of ≥ 15 mmHg from Baseline
Heart rate	≥ 120 bpm
	< 45 bpm
	Increase of ≥ 15 bpm from Baseline Decrease of ≥ 15 bpm from Baseline

Abbreviations: bpm, beats per minute; mmHg, millimeters of mercury.

9.3.4. Endometrial Biopsy

Primary diagnosis of endometrial biopsy assessment will be summarized at Baseline and at scheduled assessment by treatment group. All endometrial biopsy data will also be provided in a by-patient listing.

Primary diagnosis from pathologist evaluation will be categorized by medical monitor's review in Table 15 and will be summarized using frequencies and percentages, summarized for each treatment group. All endometrial biopsy data will also be provided in by-patient listings.

Table 15: Categories of Primary Diagnosis in Endometrial Biopsies

Normal-Proliferative	• Weakly proliferative • Proliferative • Disordered proliferative
Normal-Secretory/Menstrual/Mixed	• Secretory • Menstrual • Progestational/Decidulized/Mixed
Normal-Atrophic or Minimally Stimulated	• Atrophic • Indeterminate/Inactive
Hyperplasia	• Simple hyperplasia without atypia • Simple hyperplasia with atypia • Complex hyperplasia without atypia • Complex hyperplasia with atypia
Carcinoma	—
Inadequate	—
Missing	—
Additional Diagnosis (Other reported finding)	• Reactive/Inflammatory • Polyp • Metaplasia • Glandular and/or Stromal Breakdown

9.3.5. Bone Mineral Density

Corrected BMD data will be used for analysis as determined by the central radiology laboratory in the 3 prespecified anatomical locations: lumbar spine (L1–L4), total hip, and femoral neck.

BMD at Baseline, Week 12 and Week 24 visits will be summarized descriptively by treatment group and each anatomical location. Percentage changes from Baseline along with 95% CIs of mean percentage changes will be also summarized by treatment group and anatomical location. Mean percentage change from Baseline with its corresponding 95% CI will be plotted by visit, treatment group, and anatomical location.

To support the inclusion of E2/NETA in the treatment regimen, the safety endpoint of mean percent change from Baseline in BMD at the lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal

comparison of the relugolix + E2/NETA group (Group A) versus the relugolix + delayed E2/NETA group (Group B) (details in the Integrated Summary of Safety Statistical Analysis Plan).

In addition, the difference of percentage change from Baseline between treatment groups (relugolix + E2/NETA group versus the relugolix + delayed E2/NETA group at 12 weeks, relugolix + E2/NETA versus placebo group at 12 and 24 weeks, and relugolix + delayed E2/NETA group versus placebo group at 12 weeks) will be summarized at each visit by anatomical location along with the corresponding 95% CIs.

To account for participants whose BMD assessment may have been obtained outside of the protocol-specified window (Week 12 ± 3 weeks, Week 24 ± 3 and 4 weeks), a sensitivity analysis by visit will be conducted that includes all women who underwent DXA at both time points, regardless of whether the image was procured during the prespecified time window.

A mixed-effects model with repeated measures will be used to describe treatment effect on BMD at 12 and 24 weeks. The model will have treatment group, age at Baseline, visit, Baseline BMD value, stratification factors (geographic region and menstrual blood loss volume), race (African American versus Other), and BMI at Baseline as fixed effects using an unstructured variance-covariance matrix. Least square means on each anatomical location will be presented and plotted at each visit with associated 95% CIs. Categorical representation of percentage change from Baseline to 12 and 24 weeks of treatment will be presented by the number and proportion of patients who had BMD declines of ≤ 2%, >2% to 3%, > 3% to 5%, > 5% to 8%, and > 8% by treatment group and anatomical location. The 95% CIs will be provided for the respective proportions.

Categorical changes from Baseline in overall BMD (defined as lumbar spine and total hip) also will be assessed at 12 and 24 weeks. Femoral neck evaluates a smaller area of bone mass than the total hip and is prone to lower precision in the measurement (ISCD Official Positions, 2015; Leslie, 2007). Since femoral neck BMD may be associated with discordant readings compared with the total hip or lumbar spine due to technical considerations, it will not add meaningful interpretation of overall BMD changes in response to treatment.

Z-scores will be summarized by treatment group, visit, and anatomical location with descriptive statistics including 95% CIs, and the number and percentage of patients with a Z-score < -2.0 will be presented by treatment group, visit, and anatomical location.

BMD percentage changes from Baseline will also be summarized by intrinsic factors (eg, age, race, body mass index) and extrinsic factors (eg, geographic region).

9.3.6. Bleeding Pattern

Bleeding patterns will be summarized at Week 24/EOT by treatment group. Three bleeding patterns will be considered: amenorrhea (see Section 7.4.3), cyclic bleeding, and irregular bleeding. Patients with the cyclic bleeding pattern are those who do not meet the definition of amenorrhea and do meet the following conditions:

- 3 to ≤ 12 days of menstruation duration per eDiary at Week 24/EOT window (see Section 7.3.3)

- No more than 2 days of gap of no bleeding (per eDiary) within the menstruation duration.

Patients with the irregular bleeding pattern are those who do not meet the definitions of cyclic bleeding or amenorrhea. The number (and percent) of patients and mean number of bleeding days will be provided by treatment group for each bleeding pattern.

For patients with cyclic or irregular bleeding pattern, the number (and percent) of patients with observed MBL volume falling into the following bleeding intensity groups will be provided:

- **Spotting/negligible bleeding:** MBL volume < 5 mL
- **Light:** MBL volume 10 - 50 mL
- **Moderate:** MBL volume >50 to ≤80 mL
- **Heavy:** MBL volume > 80 mL

For each bleeding intensity category, the mean number of bleeding days will be summarized.

10. REFERENCES

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APPENDICES

APPENDIX 1. SUMMARY OF SECONDARY ENDPOINT ANALYSES

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
Key Secondary Efficacy Endpoints with Alpha Protection					
Proportion of women who achieve amenorrhea over the last 35 days of treatment	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Week 24	Frequency and percentages
% change from Baseline to Week 24 in MBL volume	mITT	Mixed-effects model	P < 0.05	Week 24	LS means for % change
Proportion of women with a hemoglobin ≤10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24	Subset of mITT	Cochran-Mantel-Haenszel test	P < 0.05	Week 24	Frequency and percentages
Change from Baseline to Week 24 in the UFS-QoL Bleeding and Pelvic Discomfort Scale score, a sub-scale of the UFS-QoL Symptom Severity Scale	mITT	Mixed-effects model	P < 0.05	Week 24	LS means for change
Proportion of patients with a maximum NRS score ≤ 1 during the 35 days before the last dose of study drug in the subset of women with a maximum NRS score ≥4 for pain associated with uterine fibroids during the 35 days prior to randomization	Subset of mITT	Cochran-Mantel-Haenszel test	P < 0.05	Week 24/EOT	Frequency and percentages
% change from Baseline to Week 24 in uterine fibroid volume	mITT	ANCOVA model	P < 0.05	Week 24	LS means for % change
% change from Baseline to Week 24 in uterine volume	mITT	ANCOVA model	P < 0.05	Week 24	LS means for % change
Other Secondary Efficacy Endpoints					
Time to achieve MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume as measured by the alkaline hematin method	mITT	Log-rank test/KM method	P < 0.05	Monthly	KM estimates at Week 12 and 24, KM plots, median time to response
Time to achieve amenorrhea	mITT	Log-rank test/KM method	P < 0.05	Monthly	KM plots, median time to response

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
Time to sustained amenorrhea	mITT	Log-rank test/KM method	P < 0.05	Monthly	KM plots, median time to response
Proportion of women in the relugolix Group A versus the placebo Group C who achieve an MBL volume of < 80 mL AND at least a 50% reduction from Baseline MBL volume at Week 4, Week 12, Week 16, and Week 20	mITT	No comparison		*at Week 4, Week 12, Week 16, and Week 20*	Descriptive
Sustained amenorrhea rate by visit	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Change (absolute and %) from Baseline to Week 24 in hemoglobin for women with a hemoglobin ≤ 10.5g/dL at Baseline	mITT	Mixed-effects model	P < 0.05	Monthly	LS means for % change
Proportion of women who achieve a maximum Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization	Subset of mITT	Cochran-Mantel-Haenszel test	P < 0.05,	Week 12, 24	Frequency and percentages
Mean maximum NRS scores over time	Subset of mITT	Descriptive		Monthly	Means
Proportion of responders who had meaningful reduction of >20 points from Baseline to Week 24 in UFS-QOL Bleeding and Pelvic Discomfort Scale (Q1, Q2 and Q5)	mITT	Cochran-Mantel-Haenszel test	P < 0.05,	Week 12, 24	Frequency and percentages
Proportion of responders who had meaningful increase of > 20 points from Baseline to Week 24 in UFS-QOL revised activities	mITT	Cochran-Mantel-Haenszel test	P < 0.05,	Week 12, 24	Frequency and percentages

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL revised activities domain	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Q11	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Q20	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Q29	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the UFS-QoL Symptom Severity Scale score	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change from Baseline to Week 24 in the UFS-HRQL total score	mITT	Mixed-effects model	P < 0.05	Week 12, 24	LS means for change
Change in PGA for uterine fibroid related function from Baseline to Week 24	mITT	Mixed-effects model	P <0.05	Monthly	LS means for absolute and change
Change in PGA for uterine fibroid symptoms from Baseline to Week 24	mITT	Mixed-effects model	P < 0.05	Monthly	LS means for absolute and change
Proportion of patients achieving improvement in PGA for uterine fibroid symptoms from Baseline to Week 24	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Proportion of patients achieving improvement in PGA for uterine fibroid related function from Baseline to Week 24	mITT	Cochran-Mantel-Haenszel test	P < 0.05	Monthly	Frequency and percentages
Safety Related Endpoints					
% Change from Baseline to Week 12 in BMD (pooled data)	Safety population	Mixed-effects model Relugolix Group A vs B	P < 0.05,	Week 12	LS means Diff (95%CI)

Secondary Endpoints	Analysis Population	Statistical Method/Test	Declare Statistical Significance [a]	Time Points of Summary	Summary Statistics
% Change from Baseline in BMD	Safety population	Mixed-effects model Relugolix Group A vs Placebo at 12/24 weeks; Relugolix Group B vs Placebo at 12 weeks		Week 12, 24	LS means Diff (95%CI)
Exploratory Secondary Efficacy Endpoints					
Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities	mITT	Descriptive		Monthly	Frequency and percentages
Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities	mITT	Descriptive		Monthly	Frequency and percentages

Abbreviations: KM, Kaplan-Meier; LS, least squares; mITT, modified intent-to-treat; NRS, Numerical Rating Scale; Q, question; UFS-HRQL, Uterine Fibroid Scale – Health-related Quality of Life.

[a] P-values are two-sided.

APPENDIX 2. DERIVATION AND PSYCHOMETRIC EVALUATION OF A UFS-QOL BLEEDING AND PELVIC DISCOMFORT SCALE

The BPD Scale was derived from the Symptom Severity Scale of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL). The BPD Scale consists of three items proximal to uterine fibroids that are experienced by most patients, (ie, heavy bleeding during the menstrual period [Question 1], passing blood clots during the menstrual period [Question 2], and feeling tightness or pressure in the pelvic area [Question 5]).

The aim of this appendix is to describe the derivation and psychometric testing process of the BPD Scale. Results of the analyses in this appendix are summarized in Appendix 3 and will be included in the Patient-Reported Outcomes dossier to be submitted at the time of filing for the uterine fibroids registration program.

Exploratory factor analysis and subsequent confirmatory factor analysis were conducted to assess and confirm the factor structure of the Symptom Severity Scale of the UFS-QoL, using data from a phase 2 study of relugolix in uterine fibroids (TAK-385/CCT-001), as well as pooled, blinded data from one-third of patients in the phase 3 studies (MVT-601-3001 and MVT-601-3002). Respective analyses are described in Section 2.1. Based on the results, the factor(s) reflecting symptoms proximal to uterine fibroids and experienced by most patients with uterine fibroids were selected for further psychometric testing.

The psychometric properties of the new scale were assessed using the same pooled, blinded data from the two phase 3 studies of relugolix in uterine fibroids (MVT-601-3001 and MVT-601-3002). These analyses are described in Section 2.2. The blinded data consists of the first third of patients (approximately n = 260) enrolled into the two pivotal studies who have completed the patient global assessment (PGA) for symptoms and the UFS-QoL at Baseline and at Week 24. Of note, for the analyses specified in Section 2.2, only data at Baseline and Week 12 were used; the Week 24 data was used in the responder analyses described in Appendix 3.

2.1. Development of the Bleeding and Pelvic Discomfort Scale Using Phase 2 and Phase 3 Data

From a review of the eight items in the Symptom Severity Scale of the UFS-QoL, it was apparent that the scale consists of different constructs/dimensions. Therefore, the factor structure of the Symptom Severity Scale was assessed, initially using data from the phase 2 study TAK-385/CCT-001 (n = 216).

Of note, in the TAK-385/CCT-001 phase 2 study, the UFS-QoL with a one-month recall period was applied, whereas the UFS-QoL with a three-month recall period is used in the phase 3 studies (MVT-601-3001 and MVT-601-3002). Therefore, confirmatory factor analysis and final psychometric testing of the chosen factor was conducted using blinded phase 3 data (see Section 2.2).

Exploratory Factor Analysis

The exploratory factor analysis was done on phase 2 data to identify the underlying constructs by the most parsimonious factor structure of the eight items in the Symptom Severity Scale. Identification of the number of factors was based on the following criteria:

- Items with primary factor loading > 0.4;
- Factors with large eigenvalues considered as common factors using Kaiser criterion (Kaiser, 1960).

A scree plot was used as a supplemental tool to decide on the number of factors in the final model.

Confirmatory Factor Analysis

Once the number of factors was identified, a confirmatory factor analysis was conducted using blinded, pooled phase 3 data to confirm the factor structure. Only patients who completed the Baseline and Week 24 PGA for symptoms and UFS-QoL assessments were included in this analysis. Model fit was assessed based on the following:

- The goodness of fit as measured by χ^2 and Goodness of Fit Index; a Goodness of Fit Index > 0.9 is considered acceptable;
- The Comparative Fit Index was used to determine the acceptability of the model fit of the discrepancy function adjusted sample size; a Comparative Fit Index > 0.9 (Hu, 1995) was considered an acceptable fit;
- The root mean square error of approximation was used to determine the acceptability of model fit of the square root of the discrepancy between the sample covariance matrix and the model covariance matrix; the root mean square error of approximation had to be < 0.06 (Browne, 1993) to be considered an acceptable fit;
- P-value > 0.05.

Once the final factor structure was identified, the factor reflecting items proximal to uterine fibroids and experienced by almost all patients with uterine fibroids were selected for further evaluation. Of note, this was the BPD Scale.

2.2. Psychometric Analyses Based on Phase 3 Data

The same pooled, blinded data from the first third of patients enrolled in either of the two phase 3 studies (MVT-601-3001 or MVT-601-3002) was used for the psychometric analyses of the BPD Scale. The objective was to psychometrically evaluate the new scale in terms of item performance, reliability, validity, and ability to detect change. Of note, for the analyses specified in this section, only data at Baseline and Week 12 were used. The following analyses were performed:

Item Level Analysis Assessing Ceiling and Floor Effects:

- A descriptive summary of the eight items in the UFS-QoL Symptom Severity Scale at Baseline was provided to examine item distributions and ceiling/floor effects. Low ceiling effects (< 20%) and higher floor effects (> 20%) were expected at Baseline

due to symptom severity of patients with uterine fibroids enrolled in the phase 3 studies.

Internal Consistency:

Internal consistency reliability was assessed for the BPD Scale at Baseline and Week 12 by calculating Cronbach's alpha. Generally, a Cronbach's alpha coefficient (α) $\geq$ 0.7 indicates an acceptable level of internal consistency.

Item Performance:

- Intercorrelation of items that contribute to the BPD Scale by means of item-total correlation was determined.
- Item discrimination index was assessed for each item based on 1) the BPD Scale scores at single time points, and 2) the change from Baseline to Week 12 in the BPD Scale score to determine the degree to which individual items were able to discriminate between less and more severe patients (Cappelleri, 2014).

Known-Groups Validity:

- Known-groups validity was assessed based on groups defined by Baseline PGA for symptoms severity (five levels). Descriptive statistics of the BPD Scale will be provided for each severity level.

Ability to Detect Change:

Evidence that the new scale can identify differences in scores over time in individuals or groups who have changed with respect to the measurement concept will be investigated by providing the following descriptive statistics:

- Within person change from Baseline to Week 12 in each item on the BPD Scale
- Standardized effect size statistic (SES) for change from Baseline to Week 12 in each item scale. The ability to detect change will be judged based on Cohen's recommendations: small change (SES = 0.20), moderate change (SES = 0.50), and large change (SES = 0.80).

2.3. References

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APPENDIX 3. DERIVATION AND VALIDATION OF THE UFS-QOL BLEEDING AND PELVIC DISCOMFORT SCALE

Results described in this appendix are based on the analyses described in Appendix 2.

3.1. Development of the Bleeding and Pelvic Discomfort Scale Using Exploratory and Confirmatory Factor Analysis

Exploratory factor analysis was conducted on data from the phase 2 study TAK-385/CCT-001 study (n = 216) and the arising factor structure was assessed in a confirmatory factor analysis using data from the phase 3 studies MVT-601-3001 and MVT-601-3002.

3.1.1. Exploratory Factor Analysis Using Phase 2 Data

Exploratory factor analysis results revealed a two-factor solution based on the Kaiser criterion (eigenvalues > 1) and factor loading > 0.40 criteria specified in the analysis plan (see Appendix 2). Factor 1 and Factor 2 had eigenvalues of 3.394 and 1.196, respectively (Table 3.1-1). Three items were found to load adequately onto Factor 1 with loadings greater than 0.40: Item 1 (Heavy Bleeding during Your Period), Item 2 (Passing Blood Clots during Your Period), and Item 5 (Feeling Tightness or Pressure in Pelvis; see Table 3.1-2). Two items loaded onto Factor 2 with loadings larger than the prespecified level: Item 6 (Frequent Urination in Daytime) and Item 7 (Frequent Nighttime Urination). Item 8 (Feeling Fatigued) showed a loading value on Factor 1 just below the prespecified threshold (0.399) and showed evidence of cross-loading with the Factor 2 (0.288). An additional factor with a moderate eigenvalue (0.62) was considered based the scree plot (Figure 3.1-1) and factor loadings of its associated items (Item 3: Fluctuation in Duration of Menstruation, 0.416; Item 4: Fluctuation in Length of Monthly Cycle, 0.995; Table 3.1-2).

Overall the results show support for a seven-item three-factor model. Due to multi-factor loading, Item 8 (Feeling Fatigued) remains a single-item symptom and is not scored as part of any factor.

Figure 3.1-1: Scree Plot and Variance Explained for UFS-QoL Symptom Severity Scale Factors in TAK-385/CCT-001

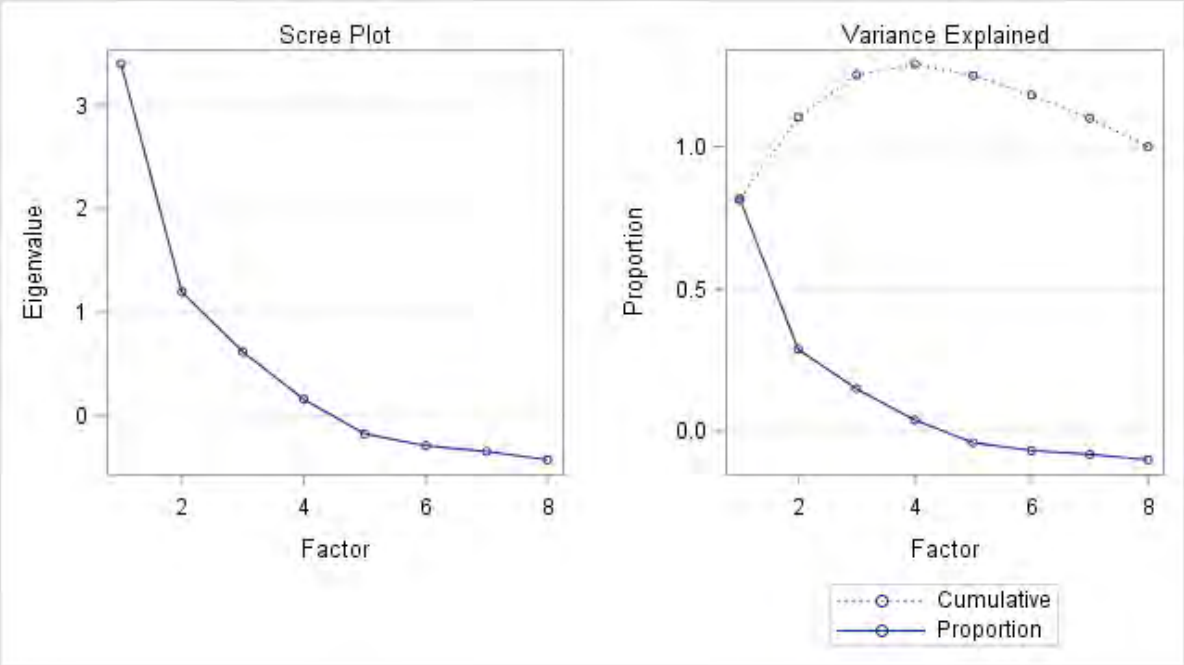


Table 3.1-1: Exploratory Factor Analysis for the UFS-QoL Symptom Severity Scale in TAK-385/CCT-001

Item	Eigenvalue	Difference	Proportion	Cumulative
1	3.394	2.198	0.816	0.816
2	1.196	0.576	0.288	1.104
3	0.620	0.458	0.149	1.253
4	0.162	0.332	0.039	1.292
5	-0.170	0.114	-0.041	1.251
6	-0.284	0.057	-0.068	1.183
7	-0.341	0.079	-0.082	1.101
8	-0.419	—	-0.101	1.000

Table 3.1-2: Factor Loadings for the UFS-QoL Symptom Severity Scale in TAK-385/CCT-001

Items		Factor1	Factor2	Factor3
Q2	Passing blood clots during your period	**0.763**	0.105	0.073
Q1	Heavy bleeding during your period	**0.759**	0.091	0.123
Q5	Feeling tightness or pressure in pelvis	**0.467**	0.175	0.167
Q8	Feeling fatigued	0.399	0.288	0.078
Q6	Frequent urination in daytime	0.114	**0.965**	0.069
Q7	Frequent nighttime urination	0.212	**0.630**	0.013
Q4	Fluctuation in length of monthly cycle	0.039	0.092	**0.995**
Q3	Fluctuation in duration of menstruation	0.178	0.003	**0.416**

Extraction method: maximum likelihood. Rotation method: orthogonal.

3.2. Development of the Bleeding and Pelvic Discomfort Scale Using Confirmatory Factor Analysis Based on Phase 3 Data

The exploratory factor structure arising from the phase 2 data was assessed using data from the phase 3 studies MVT-601-3001 and MVT-601-3002.

Analyses were based on pooled, blinded data from the first one third of patients enrolled in the two phase 3 studies of relugolix in uterine fibroids (MVT-601-3001 and MVT-601-3002), who completed the patient global assessment of symptoms (PGA) and the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) at Baseline and at Week 24.

3.2.1. Confirmatory Factor Analysis using Phase 3 Data

A confirmatory factor analysis was completed using blinded data from one third of phase 3 patients. The acceptance criteria of the confirmatory factor analysis were prespecified as a Goodness of Fit Index > 0.90 and a Comparative Fit Index > 0.90, a root mean square error of approximation < 0.06 and a non-significant p-value to show that the null-hypothesis that the data fits the three-factor model was not rejected (Table 3.2-1).

Factor loadings for the seven-item three-factor model supported the three-factor solution proposed by the exploratory factor analysis in the above described analyses using phase 2 data. Results indicated that the three-factor model, excluding item 8, had a Goodness of Fit Index and a Comparative Fit Index of 1.00 and a root mean square error of approximation of 0.00 (90% CI = 0.00-0.02). The test of model fit returned a p-value of 0.9394. The null hypothesis that the data fit the model was not rejected (see Table 3.2-1). Under this model, Item 5 (Feeling Tightness or Pressure in Pelvis) also cross-loaded onto Factor 2, assessing urinary symptoms.

Table 3.2-1: Confirmatory Factor Analysis of the UFS-QoL Symptom Severity Scale without Item 8: Model Fit Statistics at Baseline (MVT-601-3001 and -3002)

Model Fit Statistics[a]					
Model		**CFI**	**RMSEA (90%CI)**	**GFI**	**P-value**
3-Factor Model (7-item)		1.000	0.000 (0.00-0.02)	1.000	0.9394
Factor Loading[b]					
			Factor1	**Factor2**	**Factor3**
Q1	Heavy bleeding during your period		**0.7314**	0.2672	0.2024
Q2	Passing blood clots during your period		**0.7620**	0.1503	0.2099
Q3	Fluctuation in duration of menstruation		0.3263	0.1861	**0.6909**
Q4	Fluctuation in length of monthly cycle		0.1689	0.1561	**1.0323**
Q5	Feeling tightness or pressure in pelvis		**0.4644**	**0.4657**	0.1965
Q6	Frequent urination in daytime		0.2503	**0.7727**	0.1300
Q7	Frequent night time urination		0.1553	**0.8605**	0.1538

Abbreviations: CFI, comparative fit index; CI, confidence interval; GFI, goodness of fit index; RMSEA, root mean square error approximation.

[a] Model fit statistics allow for assessment of the model appropriateness.

[b] Rotation Method: Orthogonal.

In order to further assess the performance of the Fatigue item, which was excluded following the exploratory factor analysis due to cross-loading, the confirmatory factor analysis was reconducted with the inclusion of this item in Factor 1. Results showed that the eight-item three-factor model had a Goodness of Fit Index of 0.996, a Comparative Fit Index of 1.00 and a root mean square error of approximation of 0.00 (90% CI = 0.00-0.05). The test of model fit returned a p-value of 0.8056. However, the results for Item 8 showed a cross-loading of this item at 0.417 on Factor 1 and 0.437 on Factor 2 (Table 3.2-2). This continued cross-loading supports the exclusion of this item in the scoring of any factor (Table 3.2-2).

Table 3.2-2: Confirmatory Factor Analysis of the UFS-QoL Symptom Severity Scale with Item 8 included: Model Fit Statistics at Baseline (MVT-601-3001 and 3002)

Model Fit Statistics[a]					
Model		**CFI**	**RMSEA (90%CI)**	**GFI**	**P-value**
3-Factor Model (8-item)		1.000	0.000 (0.00-0.05)	0.996	0.8056
Factor Loading[b]					
			Factor1	Factor2	Factor3
Q1	Heavy bleeding during your period		**0.732**	0.265	0.211
Q2	Passing blood clots during your period		**0.750**	0.150	0.226
Q3	Fluctuation in duration of menstruation		0.296	0.175	**0.767**
Q4	Fluctuation in length of monthly cycle		0.180	0.167	**0.932**
Q5	Feeling tightness or pressure in pelvis		**0.473**	**0.465**	0.206
Q6	Frequent urination in daytime		0.251	**0.757**	0.137
Q7	Frequent night time urination		0.150	**0.876**	0.156
Q8	Feeling fatigued		**0.417**	**0.437**	0.136

Abbreviations: CFI, comparative fit index; CI, confidence interval; GFI, goodness of fit index; Q, question; RMSEA, root mean square error of approximation.

[a] Model fit statistics allow for assessment of the model appropriateness.

[b] Rotation Method: Orthogonal.

3.3. Classical Test Theory Psychometric Analyses of the Bleeding and Pelvic Discomfort Scale Based on Phase 3 Data

Each of the above-described factor analyses showed that a seven-item three-factor solution was appropriate for the UFS-QoL Symptom Severity Scale. Following this confirmation, blinded psychometric appraisal of the measure was implemented to further understand the performance of the items and subscales of the UFS-QoL Symptom Severity Scale. For the item level analysis, all items were assessed. For subscale level analysis, the analysis was focused, primarily, on the evaluation of the Factor 1 – the Bleeding and Pelvic Discomfort (BPD) Scale. The BPD Scale was selected as the primary focus for further psychometric evaluation, as it presents clinical and patient-reported symptoms proximal to the disease and is associated with high symptom burden experienced by most patients.

Analyses were based on pooled, blinded data from the first one third of patients enrolled in the two phase 3 studies of relugolix in UF (MVT-601-3001 and MVT-601-3002) who completed the PGA for symptoms and the UFS-QoL at Baseline and at Week 24. Of note, for the analyses specified in this section, only data at Baseline and Week 12 were used.

3.3.1. Item Level Analysis of the UFS-QoL Symptom Severity Scale

UFS-QoL Symptom Severity Scale item responses were assessed for floor (highest possible severity) and ceiling effects (lowest possible severity). Overall, the measure showed no ceiling effects (response option 1, Table 3.3-1, demonstrating that the items have scope to capture

patient improvement in disease burden. A greater proportion of patients responded at floor level (response option 5; range =11.15 to 36.15%), which is expected at the start of a clinical trial. All response options for all items were used, showing a good coverage of the range of disease burden. When considering BPD Scale items, all items showed a range of responses that covered the response scale, with over 50% of patients reporting being a (very) great deal distressed by heavy bleeding during menstrual period (Item 1), passing blot clots during menstrual period (Item 2), and feeling of tightness or pressure in the pelvic area (Item 5).

Table 3.3-1: Summary of UFS-QoL Symptom Severity Scale Response at Baseline by Items in MVT-601-3001 and 3002

	Q1 (N = 260)		Q2 (N = 260)		Q3 (N = 260)		Q4 (N = 260)		Q5 (N = 260)		Q6 (N = 260)		Q7 (N = 260)		Q8 (N = 260)	
Response	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1	4	(1.54%)	4	(1.54%)	44	(16.92%)	63	(24.23%)	21	(8.08%)	48	(18.46%)	54	(20.77%)	13	(5.00%)
2	15	(5.77%)	30	(11.54%)	48	(18.46%)	37	(14.23%)	24	(9.23%)	35	(13.46%)	53	(20.38%)	21	(8.08%)
3	53	(20.38%)	61	(23.46%)	66	(25.38%)	69	(26.54%)	57	(21.92%)	77	(29.62%)	64	(24.62%)	59	(22.69%)
4	101	(38.85%)	71	(27.31%)	64	(24.62%)	62	(23.85%)	96	(36.92%)	62	(23.85%)	55	(21.15%)	82	(31.54%)
5	87	(33.46%)	94	(36.15%)	38	(14.62%)	29	(11.15%)	62	(23.85%)	38	(14.62%)	34	(13.08%)	85	(32.69%)

Abbreviations: N, number of patients; n, number of patients in subset; Q, question.

3.3.2. Scale Level Analysis of the BPD Scale

3.3.2.1. Internal Consistency

Internal consistency was assessed for the BPD Scale at Baseline and Week 12. Reliability was acceptable at Baseline (> 0.70) and good at Week 12 (> 0.80; Table 3.3-2).

Table 3.3-2: Cronbach's Alpha Coefficient of BPD Scale by VISIT (MVT-601-3001 and 3002)

		Q1	Q2	Q3	
	n	Mean (SD)	Mean (SD)	Mean (SD)	**Alpha[a]**
Baseline	260	3.97 (0.95)	3.85 (1.09)	3.59 (1.18)	0.768
Week 12	258	2.75 (1.47)	2.69 (1.46)	2.64 (1.36)	0.882

Abbreviations: n, number of patients; Q, question; SD, standard deviation.
[a] Cronbach Coefficient Alpha

3.3.2.2. Item-to-Total Correlations

Item-to-total correlations were assessed to ensure that each item was associated with the BPD Scale score. Correlations demonstrate that each of the items have a strong relationship with the total score at Baseline and at Week 12 ($r > 0.50$) (Table 3.3-3). Correlations improved at Week 12, which represents a greater spread of the data across each item's five-point response scale, further supporting the relationship of these items to the BPD total score.

Table 3.3-3: Intercorrelation of Items in BPD Scale by Visit (MVT-601-3001 and 3002)

Question	**Baseline** **N = 260**	**Week 12** N = 258
Q1	0.670	0.802
Q2	0.620	0.845
Q5	0.533	0.674

Note: Intercorrelation calculated using Pearson's correlations.

3.3.2.3. Item Discrimination Indices

An item discrimination index was employed to assess the ability of each item to discriminate between high and low severity patients. At Baseline, the discrimination index represents each item's ability to differentiate patients on the BPD Scale scores at a single time point, and at Week 12, the discrimination index represents the ability to differentiate patients based on their level of change from Baseline to Week 12 in the BPD Scale score.

Results show that all items had a discrimination index above 0.60, demonstrating that BPD Scale items are able to discriminate between high- and low-severity patients both when assessing single time point scores and change over time (Table 3.3-4).

Table 3.3-4: Item Discrimination Index of BPD Scale (MVT-601-3001 and 3002)

	Q1	Q2	Q5
Baseline (n = 260)	0.815	0.954	0.923
Week 12 (n = 258)	0.915	0.986	0.836

Abbreviations: n, number of patients; Q, question.
Note: BPD scale upper/lower ranges**:** Upper = at least 65-point reduction, Lower = at most 10-point reduction.

3.3.2.4. Known-Groups Validity

A known-groups analysis assessed the descriptive BPD score and score ranges for patients stratified by level of severity reported on the PGA (symptoms). Results from the known-groups validity assessment show that mean and median BPD Scale scores increase monotonically in line with PGA symptom severity (Table 3.3-5).

3.3.2.5. Ability to Detect Change

The BPD Scale's ability to detect change was assessed though the difference in BPD Scale scores over time in patients who have changed with respect to the measurement concept as measured by the PGA (symptoms). For each PGA stratified group, within person change from Baseline to Week 12 and standardized effect size statistics (SES) for change over the same period were assessed. SES statistics judged were based on Cohen's recommendations (small change, 0.20; moderate change, 0.50; large change, 0.80).

Results showed that the mean change for improving PGA categories had a monotonically increasing pattern from patients who had a PGA change of 0 to patients who had a PGA improvement of -4 (Table 3.3-6). Worsening groups (PGA change of +1 or +2) had very low levels of mean change, with wide standard deviations around the mean due to the low sample size in these categories.

In line with expectations, the SES statistics for the improvement categories (PGA score change of -1 to -4) were large (> 0.80) compared to the moderate SES found in the patients who reported no change (PGA score change of 0; SES = 0.55).

Table 3.3-5: Summary Statistics of BPD Scale Score at Baseline by PGA (symptoms) Response (MVT-601-3001 and 3002)

	Baseline BPD Scale Score[a]						
Baseline PGA	**N**	**Mean**	**SD**	**Median**	**Q1, Q3**	**Min**	**Max**
1	7	53.57	28.81	58.33	25.00, 75.00	16.67	91.67
2	21	59.92	26.56	58.33	41.67, 75.00	8.33	100.00
3	96	62.33	21.18	66.67	41.67, 75.00	8.33	100.00
4	89	75.09	19.48	75.00	66.67, 91.67	16.67	100.00
5	47	83.51	16.53	91.67	75.00, 100.00	41.67	100.00

Abbreviations: BPD, bleeding and pelvic discomfort; max, maximum; min, minimum; N, number of patients; PGA, Patient Global Assessment; Q1, first quartile; Q3, third quartile; SD, standard deviation.
a Transformed Score.

Table 3.3-6: Summary Statistics of Change from Baseline BPD Scale Score to Week 12 by PGA (symptoms) Change from Baseline (MVT-601-3001 and 3002)

PGA Change Category[a]	N	Mean	SD	95% CI	Median	Q1, Q3	Min	Max	Effect Size[b]
-4	23	-48.19	(42.27)	(-66.47, -29.91)	-66.67	-83.33, 0.00	-100.00	25.00	-2.93
-3	50	-49.33	(33.16)	(-58.76, -39.91)	-54.17	-75.00, -25.00	-100.00	33.33	-2.41
-2	74	-27.70	(30.75)	(-34.83, -20.58)	-25.00	-41.67, 0.00	-91.67	25.00	-1.25
-1	48	-23.09	(28.57)	(-31.39, -14.79)	-16.67	-33.33, -8.33	-100.00	33.33	-1.01
0	39	-10.68	(20.32)	(-17.27, -4.10)	-8.33	-25.00, 0.00	-66.67	33.33	-0.55
1	14	1.79	(19.11)	(-9.25, 12.82)	-4.17	-16.67, 8.33	-16.67	33.33	0.07
2	6	-1.39	(29.54)	(-32.39, 29.61)	-12.50	-25.00, 16.67	-25.00	50.00	-0.05

Abbreviations: BPD, blood and pelvic discomfort; CI, confidence interval; max, maximum; min, minimum; N, number of patients; PGA, Patient Global Assessment; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Note: Statistics calculated using transformed score of BPD scale.
[a] The PGA is a five-point, single item patient-reported outcomes tool that measures patient's symptoms. The PGA change category with -4 = Marked Improvement; 0 = No Change, +4 = Markedly Worse.
[b] Standardized effect sizes are calculated as the mean divided by the standard deviation.

3.4. Conclusions

The exploratory factor analysis offered support for a three-factor solution, which included factors assessing Bleeding and Pelvic Discomfort, Urinary Symptoms, and Fluctuation in Menstruation. The Fluctuations in Menstruation factor had an eigenvalue < 1 but had items that loaded at greater than 0.40 and made theoretical sense as a construct.

The exploratory factor analysis showed that Item 8, measuring fatigue, cross-loaded on two factors (Bleeding and Pelvic Discomfort and Urinary Symptoms). Since fatigue is a multidimensional concept that can assess impacts and/or symptoms concurrently, it was not included in the final factor structure. Confirmatory factor analysis on the seven-item three-factor solution provided support for the exploratory factor structure; however, Item 5 cross-loaded between the BPD and Urinary Symptoms factors in this analysis. As Item 5 (Feeling Tightness or Pressure in Pelvis) is a proximal symptom of uterine fibroids, this item was retained as part of the BPD factor.

To ensure that fatigue was not being inappropriately excluded from the three-factor structure, an additional confirmatory factor analysis was conducted with fatigue included within the BPD factor. The inclusion of fatigue in this model continued to show the expected cross-loading of this item. This analysis confirmed that the multidimensional concept of fatigue was not suitable for inclusion in the BPD factor.

The BPD factor, which assesses symptomology most proximal to the disease, was further assessed through classical test theory psychometric evaluation. The results showed that the items of the BPD Scale work cohesively to inform the total score of the measure, and adequately distinguish between severities. At a score level, descriptive statistics were able to support the construct validity and responsiveness of the BPD Scale through showing a monotonic improvement in BPD Scale score in line with patient self-reported improvement on the PGA (symptoms). Additionally, by showing that the items of the BPD Scale perform well together, the psychometric results help to further support the inclusion of the cross-loading Item 5 on the BPD Scale.

APPENDIX 4. APPROACH TO ESTIMATING THE RESPONDER THRESHOLD OF THE UFS-QOL BLEEDING AND PELVIC DISCOMFORT SCALE

The Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort (UFS-QoL BPD) Scale includes the following items:

During the previous 3 months, how distressed were you by:

- Heavy bleeding during your menstrual period;
- Passing blood clots during your menstrual period;
- Feeling tightness or pressure in your pelvic area.

Response options include:

- Not at all;
- A little bit;
- Somewhat;
- A great deal;
- A very great deal.

The summary score of the three items included in the UFS-QoL BPD Scale ranges from 0 to 100, where a higher score indicates a higher level of distress and a lower score indicates a lower level of distress.

Change from Baseline to Week 24 in the BPD Scale score is an alpha-protected key secondary endpoint of the pivotal studies (MVT-601-3001 and MVT-601-3002) to evaluate the treatment benefit of relugolix + E2/NETA (Group A) compared with placebo (Group C). Additionally, a responder analysis will be performed between the two groups with respect to proportion of patients who have achieved a meaningful reduction from Baseline to Week 24 in BPD Scale score. This appendix describes the approach used to derive the responder threshold, including both the quantitative and supportive qualitative methods and the respective results.

The meaningful change threshold is the smallest reduction in the BPD Scale score that is considered meaningful by patients (Cohen, 1988; Crosby, 2003; Revicki, 2008; Cappelleri, 2014; Coon, 2018). The magnitude of a meaningful change threshold depends on the magnitude of the correlation between the BPD Scale change score and the Patient Global Assessment (PGA) of symptom severity (anchor) change and the variability of change on the BPD Scale by improvement categories on the PGA of symptom severity (described in Section 4.2.2). Several anchor-based methods will be used; however, the primary analysis will be a measure of central tendency for each improvement category (see Section 4.2.3). Anchor-based methods will use data collected on:

- The BPD Scale score at Baseline and Week 24; and
- The PGA of symptom severity score at Baseline and Week 24.

Results from the anchor-based analyses will be supported by qualitative data collected in a patient interview study (MVT-601-037), a sub-study of the phase 3 trials, in which patients from

selected sites in the United States (US) provided feedback on what they considered to be a meaningful change on the BPD Scale and the PGA of symptom severity (described in Section 4.2.4).

4.2. Statistical Analyses Plan for Estimation of the Responder Threshold

4.2.1. Anchor and Its Correlation with UFS-QoL Endpoint

The PGA of symptom severity uses a five-point verbal rating scale and asks the patient:

> "How severe were your uterine fibroids symptoms, such as heavy bleeding over the last four weeks?"
>
> Response options include:
>
> - Not severe;
> - Mildly severe;
> - Moderately severe;
> - Very severe;
> - Extremely severe.

The categorical change from Baseline to Week 24 in PGA of symptom severity score will be derived, leading to nine possible outcomes ranging from +4 (denoting worsening) to -4 (denoting improvement). The change in PGA of symptom severity at Week 24 will be used as the anchor (see Table 4.2-1).

4.2.2. Target Anchor Category

The target anchor category is the anchor category that represents the minimum meaningful change and is used as the starting point to identify potential candidates for a meaningful change threshold. For the two pivotal studies, the target anchor category will be a one-point category improvement on the PGA of symptom severity score (see Table 4.2-1), as this is typically considered as a minimal clinical important difference on a five-point Likert scale.

Table 4.2-1: Change in PGA of Symptom Severity as Anchor

Anchor	Anchor Change Category	Potential Target Anchor Change Category (To Be Used for Estimation of Meaningful Change Threshold)
Change in PGA of symptom severity	-4, -3, -2, -1 (improvement), 0 (same), +1, +2, +3, +4 (worsening)	-1-category change (improvement)

Abbreviations: PGA = patient global assessment.

4.2.3. Anchor-Based Methods

To determine the meaningful change threshold for the reduction in USF-QoL BPD Scale score, the anchor-based analyses described below will be performed.

The category (or point) change in PGA of symptom severity score will be used as the anchor to classify patients into response groups depending on their level of symptom severity change from Baseline to Week 24 (see Table 4.2-1). Uncollapsed, categorical change on the PGA will range from +4 to -4. Collapsed, categorical change will be considered based on the distribution of change categories on the PGA of symptom severity. Usually the collapsing occurs on the tails with extreme worsening (+4) or improvement (-4).

Among the anchor-based analyses described below, the within-group analysis will be primary and other analyses (including between-group analysis) are supportive.

4.2.3.1. Correlation with Anchor

Correlation between the categorical change on the PGA of symptom severity score and the change in the BPD Scale score will be evaluated at Week 24, using blinded pooled data from the first third of the enrolled patients from the two pivotal studies who have completed Week 24 visits and have the corresponding PGA of symptom severity data available (denoted as the "threshold determination analysis set"). Polyserial correlation coefficient will be used with a criteria value of > 0.30 indicating meaningful correlation (Crosby, 2003; Revicki, 2008; Cappelleri, 2014; Coon, 2018).

4.2.3.2. Within-Group Meaningful Change

Magnitude of change from Baseline to Week 24 in BPD Scale score will be calculated within each anchor category group. Changes in BPD Scale scores are negative for symptom reductions and positive for symptom increases.

Descriptive statistics (*n*, mean change, median change, 25th and 75th percentiles, standard deviation [SD], confidence interval [CI], and standardized effect size [SES]) will be reported for the changes in BPD Scale scores by anchor category. The SES will be calculated for each level of anchor category group by dividing the mean change score of BPD Scale from Baseline by the Baseline SD of the anchor category group. The impact of treatment will be judged based on Cohen's recommendations (1988): small change (SES = 0.20), moderate change (SES = 0.50), and large change (SES = 0.80). Significance associated with within-patient change will be evaluated using paired t-tests on the change in BPD Scale score separately for each level of improvement on the anchor.

4.2.3.3. Supportive Analysis of Between Group Meaningful Change Using Analysis of Variance

Analysis of variance (ANOVA) will be used to determine whether a difference in mean change scores from Baseline to Week 24 on the UFS-QoL BPD Scale exists between the categorical change groups (or the collapsed groups, as appropriate). Providing there is a significant change in UFS-QoL BPD Scale scores between the (collapsed) anchor groups, the between-group differences will be explored. Any anchor group with at least 15 patients will be included in this analysis. An anchor group with < 15 patients (usually occurring on the tails with extreme

worsening [+4] or improvement [-4]) will be collapsed with its adjacent group as appropriate. Comparison of the anchor groups of interest between the target anchor (-1 change category) and the "0 change" category will be performed using a t-test. The statistically significant difference on the BPD Scale change scores corresponding to a 1-category change on the PGA of symptom severity can be used as supportive information for estimating the meaningful change threshold.

4.2.3.4. Visualizing Cumulative Distribution Function and Probability Distribution Function Plots by Anchor Category Group

Anchor-based meaningful change will also be evaluated using cumulative distribution function (CDF) plots utilizing the Kernel smoothing for all anchor category groups, based on cumulative change in UFS-QoL BPD Scale scores for all available changes from Baseline to Week 24. Specifically, the CDF plot for each anchor category displays the probability (presented on the y-axis) of patients who have achieved a given absolute change of X or less in BPD Scale score from Baseline to Week 24 for each point change along the range of possible absolute changes (from -100 [maximum reduction] to 0 [no change] to 100 [maximum increase]) expressed on the x-axis.

Similarly, the smooth probability density function (PDF) will also be plotted for each anchor category group over the range of absolute changes in BPD Scale scores. These probabilities are plotted on the y-axis, with the BPD Scale change score on the x-axis.

The CDF and PDF curves are delineated by anchor improvement category (from -4 to +4) displaying the center and separation between the curve for the target anchor group and the curve for the group reporting no change on PGA of symptom severity. It is expected that the CDF curves will not cross between the change category groups (eg, monotonic increase from no change to slightly improved and moderately improved).

4.2.4. Determining a Meaningful Change Threshold Using the Totality-of-Evidence Approach

The meaningful change threshold will be determined using the totality of evidence from the results of above quantitative anchor-based analyses; results from the interview study (MVT-601-037) will be used as supportive evidence.

The results of these analyses and proposed thresholds will be included into the Patient-Reported Outcome dossier to be submitted at the time of filing.

4.3. Results from Anchor-Based Analyses

4.3.1. Correlation of Change in BPD with PGA of Symptom Severity

Meaningful change for the UFS-QoL BPD Scale was derived based on anchor-based methods, supported by cumulative distribution function (CDF) and probability density function (PDF) curves. To assess the suitability of the selected anchor, PGA of symptom severity, a polyserial correlation was calculated between change on the PGA from Baseline to Week 24 and the change from Baseline to Week 24 on the BPD Scale. The change in the PGA was moderately correlated (r = 0.57) with the change on the BPD Scale (Table 4.3-1). Given that the PGA is less complex than the BPD scale, this result indicates that the PGA is a suitable anchor for the BPD Scale.

4.3.2. Improvement on BPD Scale by PGA Change Category

Uncollapsed changes on the PGA were used to determine minimal meaningful improvement on the BPD Scale (Table 4.3-1). Improvement on the BPD Scale increased monotonically for all the categories from "no change (0)" to "1-category improvement (-1)" to "2-category improvement (-2)" to "3 category improvement (-3)" with nonoverlapping 95% CIs for mean change of the groups. Table 4.3-1 shows further that a 1-category improvement (-1) is associated with a 27.31-point mean improvement in the BPD Scale score at Week 24 compared with Baseline, with a 95% CI [-35.42, -19.19], a large SES = -1.21, and a median improvement of 25.00 points.

Table 4.3-1: Summary of Change from Baseline to Week 24 in UFS-QoL BPD Scale by PGA for Symptom Severity Change Category (mITT Population)

PGA Change Category	N = 255	Change in BPD					Correlation between PGA Change and BPD Change[a]
		Mean (SD)	Median	95% CI	p-value[b]	SES[c]	
4-Category deterioration (+4)	0						0.57
3-Category deterioration (+3)	2	-12.50 (5.89)	-12.5	-65.44, 40.44	0.2048	-2.12	
2-Category deterioration (+2)	2	0.00 (11.79)	0	-105.89, 105.88	1.00	0.0	
1-Category deterioration (+1)	21	-10.32 (16.22)	-8.33	-17.70, -2.93	0.0086	-0.54	
0-Category deterioration (0)	47	-9.93 (23.09)	-8.33	**-16.71**, -3.15	0.005	-0.42	
1-Category improvement (-1)	47	**-27.31** (27.62)	-25.00	-35.42, **-19.19**	< 0.0001	-1.21	
2-Category improvement (-2)	68	-42.16 (25.71)	-41.67	-48.38, -35.93	< 0.0001	-1.93	
3-Category improvement (-3)	45	-61.85 (26.62)	-66.67	-69.85, -53.85	< 0.0001	-3.25	
4-Category improvement (-4)	23	-54.35 (32.65)	-66.67	-68.47, -40.23	< 0.0001	-4.12	

Abbreviations: BPD = bleeding and pelvic discomfort; CI = confidence interval; mITT = modified intent-to-treat; PGA = patient global assessment; SD = standard deviation; SES = standardized effect size.
mITT is used to calculate change from Baseline score at Week 24 and includes patients from the mITT population who have available change from Baseline data at Week 24.

[a] Polyserial correlation coefficient between change in BPD Scale and change in PGA of symptom severity.

[b] The p-value for each individual change group is derived from a paired (within-sample) t-test assessing the difference over time.

[c] SES is calculated as the mean divided by the SD of Baseline. SES is judged as small = 0.2, moderate = 0.5, and large = 0.8 (Cohen 1988).

Table 4.3-2 highlights that the difference between the "1-category improvement" and the "no change" groups (mean = -17.38 with a 95% CI of [-27.81, -6.94]) was statistically significant (p = 0.0013) and had a moderate SES = -0.736, which also supports the notion that patients interpreted these change categories as distinct.

Patients were able to distinguish between the PGA improvement categories, as demonstrated by the nonoverlapping CIs (in Table 4.3-2) for their UFS-QoL BPD Scale scores and as illustrated

by the clear separation between the CDF curves presented in Figure 4.3-1. Since statistically significant differences existed in patient responses on the BPD Scale between the "1-category improvement (-1)" option and the "no change" and "2-category improvement (-2)" options, a 1-category improvement on the PGA was considered a meaningful target anchor category for assessing the responder threshold on the BPD Scale. Although a 2-category improvement could have been considered for deriving the meaningful change threshold, such a threshold would not qualify as being the *minimum* threshold possible. Given the statistical difference between the 1- and 2-category improvements and the fact that patients were able to distinguish between the two response options (to be taken up shortly), the evidence supports using a 1-category improvement on the PGA for estimating the minimum meaningful change threshold. This decision is also supported by qualitative evidence generated from the Exit Interview study (see Section 4.2.4).

Table 4.3-2: Summary of Change from Baseline to Week 24 in BPD Scale Between Target Anchor (-1) and No Change (0) in PGA of Symptom Severity (mITT Population)

Anchor	Categorical Change	N	Mean Change from BL	SD	95% CI	p-value[a]	Baseline SD	SES
PGA	1-category improvement (-1)	47	-27.31	27.62	-35.42, -19.19		22.63	
	No change (0)	47	-9.93	23.09	-16.71, -3.15		23.61	
	Difference		-17.38	25.46	-27.81, -6.94	0.0013		-0.736[b] -0.790[c]

Abbreviations: ANOVA = analysis of variance; BL = Baseline; BPD = bleeding and pelvic discomfort; CI = confidence interval; mITT = modified intent-to-treat; PGA = patient global assessment; SD = standard deviation; SES = standardized effect size.

[a] The p-value is based on t-test for difference in mean change in BPD score between the 2 anchor groups (-1 and 0) from the ANOVA in which the +2, +3, and +4 groups were collapsed with the +1 group due to 0 or few patients in the respective groups.

[b] SES is calculated as the mean difference divided by the SD of Baseline for no change group. They are judged as small = 0.2, moderate = 0.5, and large = 0.8 (Cohen 1988).

[c] SES calculated as the mean difference divided by the standard deviation of Baseline for pooled from all categories (Glass 1976).

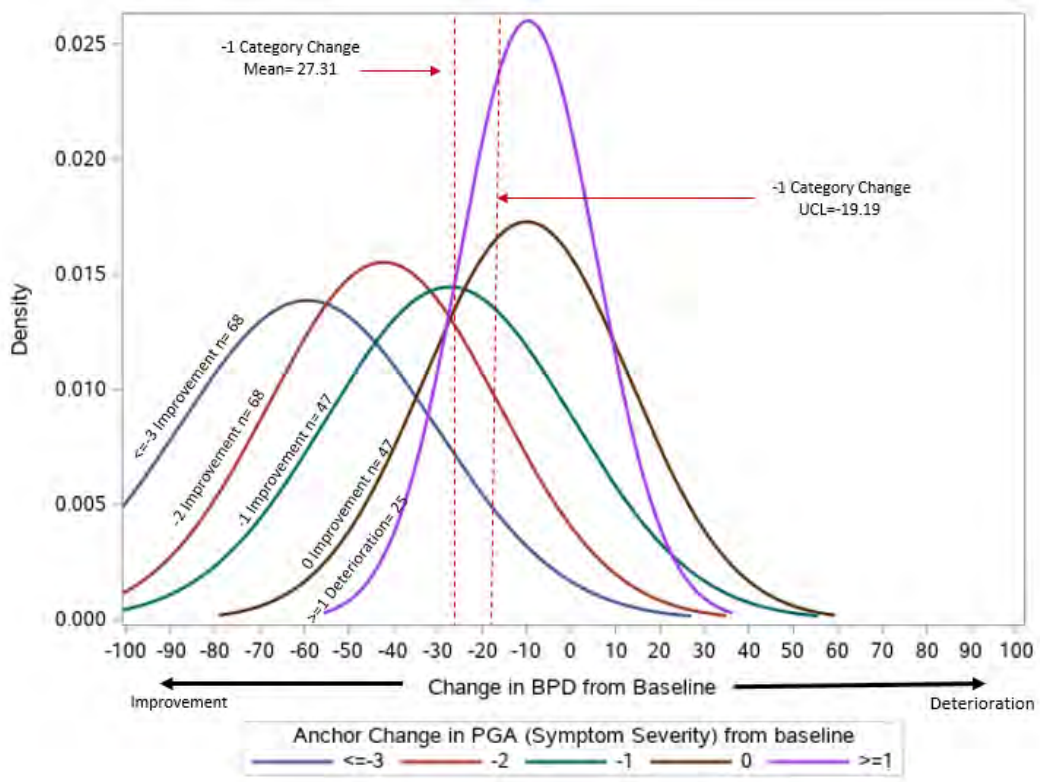
4.3.3. Estimation of Responder Threshold

Examination of the PDF curves, presented in Figure 4.3-1, indicates that the dispersion is roughly the same for the options between "> 3 category improvement" and "no change." The crossing of the "no change" and "1-category improvement" PDF curves at approximately -24 points (ie, a 24-point improvement on the BPD between Baseline and Week 24) indicates the meaningful change threshold is greater (less negative) than this value, because to the left of the value the "1-category improvement" was more probable than the "no change" curve. That is, to the left of this point (larger improvements) patients were more likely to be responders than to the right of this point. However, since the goal is to establish the minimum meaningful change threshold, the value -24 points is likely too conservative.

Using the mean or median values for measuring improvement in the BPD Scale would also yield estimates that are too conservative, because expected values do not necessarily constitute a *minimum* meaningful change threshold for patients. That is, nearly half the patients stratified in

the PGA "1-category improvement" who reported changes smaller than (to the right of) the mean or median on the BPD Scale would be classified as nonresponders by using the mean or median as the threshold despite of their reporting "1-category improvement." A less conservative, though still plausible estimate for the minimal meaningful change threshold is the upper bound of the 95% CI for mean change in the "1-category improvement" group. Its use will result in a smaller proportion of patients being classified as nonresponders in change on the BPD Scale than the expected value (ie, the mean). According to the uncollapsed anchor-based analysis (Table 4.3-1), this value is approximately -19 (ie, a 19-point improvement on the BPD Scale between Baseline and Week 24). Selection of this value is supported by the fact that the mean changes are statistically significantly different (Table 4.3-2) between "no change" and "1-category improvement" groups with clear separation of the respective 95% CIs for mean change. Of note, a value as low as -17 could also be selected, since it is less than the lower-bound 95% CI estimate of -16.71 for the "no change" group.

Figure 4.3-1: PDF of the Change in UFS-QoL BPD Scale by PGA Anchor Change Category (Collapsed)

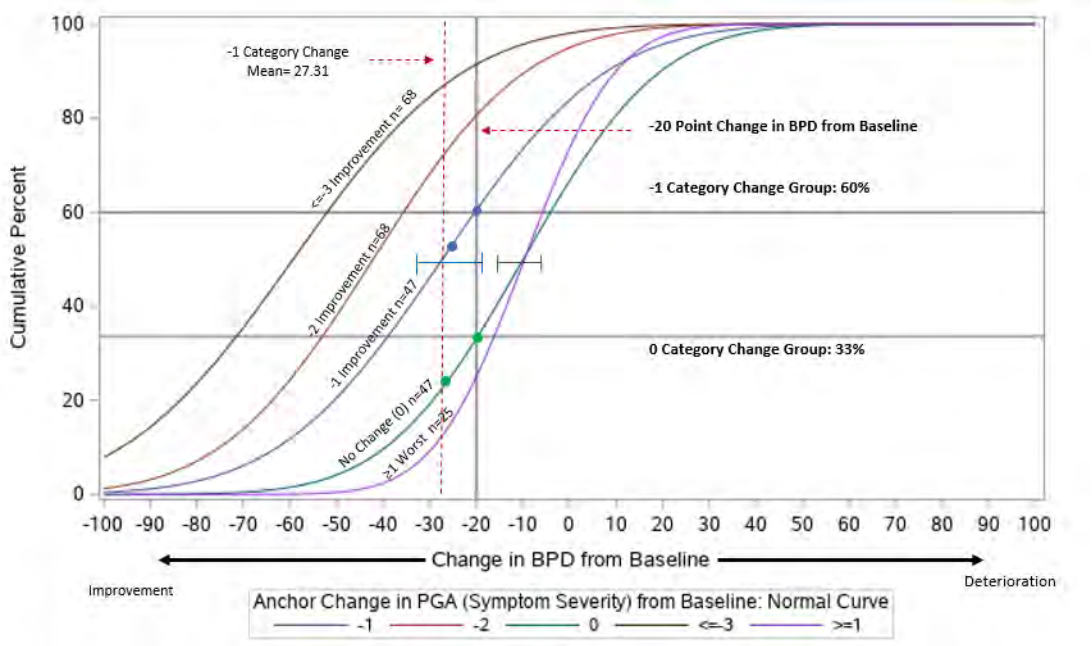


Abbreviations: BPD = bleeding and pelvic discomfort; PGA = patient global assessment; UCL = upper confidence limit.

Examination of the CDF curves for the potential minimum meaningful threshold value of -19 points on the BPD Scale allows one to estimate the cumulative percent of patients that would

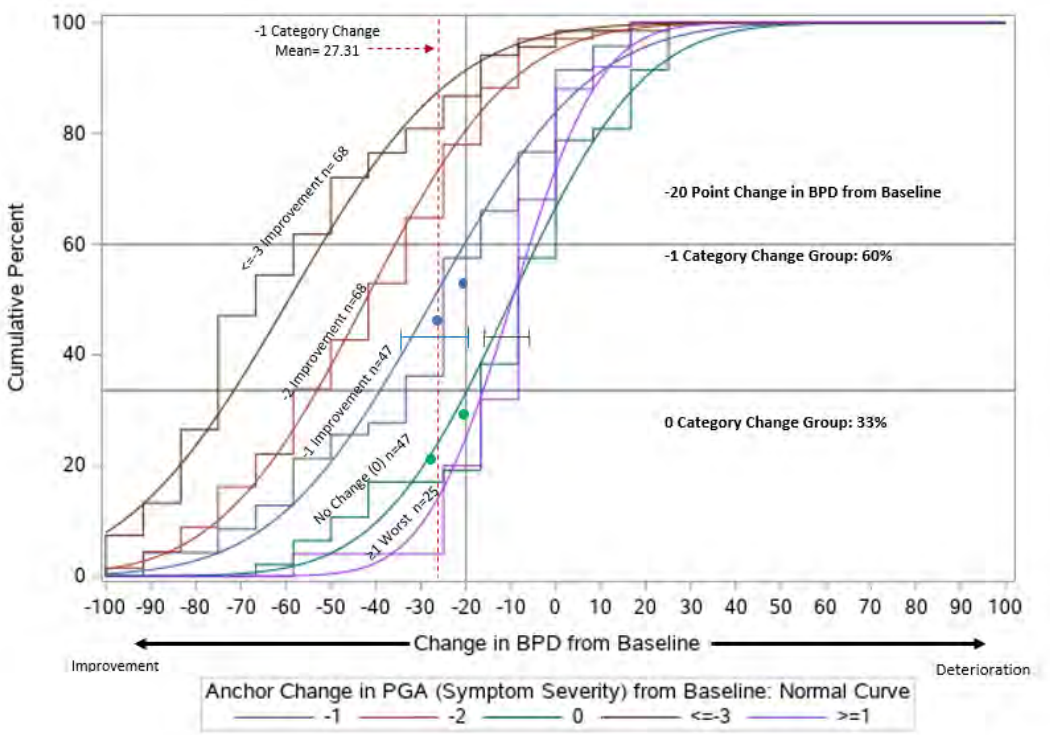
experience the improvement. As illustrated in Figure 4.3-2, approximately 35% of the "no change" group and 61% of the "1-category improvement" group experienced at least a 19-point improvement on the BPD Scale by Week 24. The high percent of patients in the "no change" group who improved on the BPD Scale by Week 24 indicates that setting the minimum meaningful change threshold at 19 points may be too liberal. The percent of misclassified responders can be improved by selecting a slightly larger value. Setting the minimum meaningful change threshold at 20-point improvement on the BPD Scale would decrease slightly the percent of misclassified responders for the "no change" group to 33% while decreasing slightly the percent of patients classified as responders to 60% for the "1-category improvement" group. As supportive information, the empirical CDFs were step-curves (reflecting the discrete nature of the BPD scores) are provided (Figure 4.3-3), indicating that smooth curves are reasonably close to the empirical CDFs.

Figure 4.3-2: Cumulative Distribution Function of Change at Week 24 in UFS-QoL BPD Scale Score by PGA Anchor Change Category (Collapsed)



Abbreviations: BPD = bleeding and pelvic discomfort; PGA = patient global assessment.

Figure 4.3-3: Empirical Cumulative Distribution Function of Change at Week 24 in UFS-QoL BPD Scale Score by PGA Anchor Change Category (Collapsed)



Abbreviations: BPD = bleeding and pelvic discomfort; PGA = patient global assessment.

4.4 Exit Interview Study Synthesis

4.4.1 Objectives

The objectives of the exit interviews were to: 1) provide qualitative evidence to understand meaningful change for patients following clinical intervention and 2) to elicit data on what patients consider to be a minimum meaningful improvement on different patient-reported outcomes (PROs), including:

- The UFS-QoL BPD Scale,
- The PGA symptoms severity.

These objectives were achieved through conducting web/Internet-based video or telephone interviews with English-speaking patients in the US within 3 to 14 days after their Week 24 visit of either ongoing phase 3 clinical study (MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]).

Minimum meaningful improvements on other PROs were also explored as part of the exit interview study; results of the respective exercises will be included in the full report for this exit interview study.

4.4.2 Methodology – Qualitative Interviews

The exit interviews were conducted via a web/Internet-based video platform (Doxy.me [https://doxy.me/]) or via telephone by trained and experienced Endpoint Outcomes interviewers.

In the event that a patient did not improve by at least 1 point from Baseline Day 1 to Week 24 based on her PGA of symptom severity scores, meaningful change exercises were not conducted for any of the PROs. An improvement on the PGA of symptom severity was required so that patients could provide contextually relevant feedback related to positive changes in uterine fibroid symptoms, as they would have experienced an improvement throughout the trial. Table 4.4-1 summarizes the measures/scales of interest, the type of data that was used in the respective meaningful change exercises, and the criteria that must have been met in order for the patient to participate in the respective meaningful change exercise.

Table 4.4-1: Overview of Procedures for Meaningful Change Exercises

Measure/Scale	Type of Data Used	Criteria That Must Have Been Met in Order to Conduct the Respective Meaningful Change Exercise
UFS-QoL BPD Scale (calculated)	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) Baseline Day 1 response	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24
PGA of symptom severity	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) responses (Baseline Day 1 and Week 24)	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24

Abbreviations: PGA = patient global assessment; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life bleeding and pelvic discomfort.

For the UFS-QoL BPD Scale, only patients' clinical study (ie, MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]) Baseline Day 1 data were used during interviews; the meaningful change discussions were hypothetical as Week 24 data were not made available to Endpoint Outcomes.[1] For the UFS-QoL BPD Scale, patients were provided with both their Baseline item-level scores and the summary score calculated based on the three items in the scale. Patients were also given a copy of the three items that comprise the UFS-QoL BPD Scale for reference during the meaningful change exercise. Patients were then presented with prespecified point change increments (ie, 10 points) and asked whether those changes reflected a meaningful improvement. If a patient indicated that a 10-point increment change would be meaningful, she was asked if an increment 5 points fewer would still be meaningful. Using a stepwise approach, interviewers then moved along the scale to identify the point at which minimum meaningful improvement was achieved for the respective patient.

For the PGA of symptom severity, patients were presented with their clinical study scores at Baseline Day 1 and Week 24 and asked if the change was meaningful. Next, patients were presented with a series of hypothetical point changes (ie, more change if the change was not

[1] For secondary endpoint data, only Baseline responses were shared with Endpoint Outcomes.

meaningful or less change if the change was meaningful, as warranted) and asked if those would be meaningful. This process continued until the minimum meaningful change on the PGA of symptom severity for that patient was identified.

Audio recordings of the interviews were transcribed verbatim and anonymized by removing identifying information such as names and places. Each transcript was considered a unit of analysis, and data from all transcripts were aggregated following coding. An initial coding scheme was developed based on the semistructured interview guide and research objectives. The coding scheme was applied and operationalized using Atlas.ti version 8.2.30 (Atlas.ti GmbH, Berlin), a software program designed specifically for qualitative data analysis. Specifically, codes were applied to selected text within each transcript and then queried for frequency across transcripts. Frequencies of patients' interview responses (eg, minimum meaningful change responses) are reported. Minimum meaningful point change medians and ranges were calculated in Excel. As the sample size for the study was small and to reduce the influence of potential outliers, the median is the preferred measure of central tendency reported.

4.4.3 Results

Thirty patients with heavy menstrual bleeding associated with uterine fibroids participated in exit interviews. The average age of these patients was 44, with ages ranging from PPD More than half of the patients (n = PPD self-reported as PPD and most patients (n = PPD were PPD In addition, the majority of patients (n = 26, 86.7%) self-reported some college or higher education as their highest education level. Two patients selected "Other" as the highest level of education and self-reported that they had medical assistant credentials.

The demographic characteristics of the patients from this exit interview study closely matched those of the LIBERTY 1 (MVT-601-3001) and LIBERTY 2 (MVT-601-3002) total sample and the LIBERTY 1 and 2 US sample (see Table 4.4-2). The average age for both the LIBERTY 1 and 2 total sample and US sample was approximately 42 years. Approximately half of participants (n = 396, 51.4%) in the total sample self-reported as black or African American, and over half of the US sample (n = 372, 63.9%) self-reported as black or African American. Additionally, most participants in both the total sample (n = 588, 76.4%) and US sample (n = 450, 77.3%) self-reported as not Hispanic or Latino. Highest level of education data was collected during patient interviews by Endpoint Outcomes; therefore, education level data for all LIBERTY 1 and 2 patients are not available.

Table 4.4-2 includes demographic data for the interviewed study sample as well as the totality of LIBERTY 1 and 2 and the US-based LIBERTY 1 and 2 sample (based on a database snapshot as of 26 Apr 2019).

Table 4.4-2: Patient Demographic Information (from Baseline MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]) and Education Information Collected during Patient Interviews

Baseline Characteristics	Exit Interview Study Sample (N = 30)	LIBERTY 1 and 2 Total Sample (N = 770)	LIBERTY 1 and 2 US Sample (N = 582)
Age (years)			
Mean (SD)	43.9 (4.5)	42.0 (5.4)	42.1 (5.2)
Range	PPD		
Race			
Black or African American	PPD	396 (51.4%)	372 (63.9%)
White		329 (44.4%)	183 (31.4%)
Ethnicity			
Not Hispanic/Latino	PPD	588 (76.4%)	450 (77.3%)
Hispanic/Latino		174 (22.6%)	130 (22.3%)
Highest level of education			
High school (no degree) or less	2 (6.7%)		
High school graduate	2 (6.7%)		
Some college (no degree)	11 (36.7%)		
Associate's degree	4 (13.3%)		
Bachelor's degree	5 (16.7%)		
Master's degree	4 (13.3%)		
Other	2 (6.7%)		

Abbreviations: SD = standard deviation.

Table 4.4-3 below summarizes the total number of exit interview study patients who completed each meaningful change exercise based on the required criteria.

Table 4.4-3: Summary of the Total Number of Exit Interview Study Patients Who Completed Each Meaningful Change Activity

Measure/Scale	Number of Exit Interview Study Patients Participating in Each Exercise (Total N = 30)[2]	Criteria that Must Have Been Met in Order to Conduct the Respective Meaningful Change Exercise
UFS-QoL BPD Scale (calculated)	25	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24
PGA of symptom severity	25	Improvement on PGA of symptom severity from Baseline Day 1 to Week 24

Abbreviations: PGA = patient global assessment; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life bleeding and pelvic discomfort.

UFS-QoL Bleeding and Pelvic Discomfort Scale

Twenty-five patients improved from Baseline Day 1 to Week 24 on the PGA of symptom severity and participated in the UFS-QoL BPD Scale meaningful change exercise. Data for 24 patients were included in the analysis as one patient provided meaningful change exercise information that was not informative and therefore was excluded from the analysis.[3] The median minimum point change considered to be a meaningful improvement was 10 points (n = 24; range = 5 to 80). The majority of patients completing the UFS-QoL BPD meaningful change activity (n = 15, 62.5%) considered a minimum change of 5 points or 10 points as meaningful (Table 4.4-4).

[2] A total of 30 patients completed exit interviews as part of this study; however, not all 30 patients completed each meaningful change exercise as additional criteria were required in order for a patient to complete the meaningful change exercises. The numbers in this table represent the total number of exit interview patients who met the criteria for participation for the specific meaningful change exercises listed.

[3] This patient did not understand how the three items comprising the UFS-QoL BPD led to the generation of her summary score and could not describe the minimum point change needed for meaningful improvement.

Table 4.4-4: UFS-QoL BPD Scale Meaningful Improvement Results

Minimum Point Change Considered to be a Meaningful Improvement	n (%) [N = 24]
5-point change	11 (45.8%)
10-point change	4 (16.7%)
15-point change	2 (8.3%)
20-point change	0 (0.0%)
25-point change	1 (4.2%)
30-point change	1 (4.2%)
35-point change	1 (4.2%)
40-point change	1 (4.2%)
45-point change	2 (8.3%)
80-point change	1 (4.2%)
Overall point change	
Median	10
Range	5 – 80

Patient Global Assessment of Symptom Severity

Twenty-five patients improved by at least 1 point from Baseline Day 1 to Week 24 on the PGA (for symptoms) and participated in the PGA of symptom severity meaningful change exercise. All patients participating in the PGA of symptom severity meaningful change exercise (n = 25, 100.0%) reported that the actual improvement experienced during the clinical study was meaningful to them.

The median minimum point change considered to be a meaningful improvement was 1 point (n = 24; range = 1 to 3); the most frequently reported minimum meaningful improvement reported by patients was a 1-point change (n = 17, 68.0%) (Table 4.4-5).

Table 4.4-5: PGA Symptom Severity Meaningful Improvement Results

Minimum Point Change Considered to Be a Meaningful Improvement	n (%) [N = 25]
1-point change	17 (68.0%)
2-point change	7 (28.0%)
3-point change	1 (4.0%)
Overall point change	
Median	1
Range	1 – 3

4.4.4 Discussion

The exit interviews provided supportive qualitative evidence to assist in the interpretation of meaningful change in patients following clinical intervention. Patients were required to improve by at least 1 point on the PGA of symptom severity over the course of the clinical study to ensure that patients interviewed had experienced improvement and could reflect upon meaningful improvements in uterine fibroid symptoms.

The decision to use actual clinical trial data in the qualitative interviews was guided by an effort to increase the contextual relevance of each of the meaningful change activities. Providing patients with their Baseline scores for the three PROs created a unique opportunity for patients to reflect on their experience since starting treatment, thereby making the exercises more relevant to them. Further, participation in the meaningful change exercises was predicated on experiencing an improvement in uterine fibroid symptoms over the course of the study, which ensured that patients could speak to meaningful changes stemming from their personal experience. This was confirmed, as all patients participating in the PGA of symptom severity meaningful change exercise (n = 25, 100.0%) reported that the change during the trial was meaningful to them.

These qualitative findings provide patient insight which can be used to supplement psychometric analyses to determine target anchor categories (for the PGA of symptom severity) and responder definitions for the UFS-QoL BPD Scale.

4.5. Determination of Responder Threshold via Triangulation of Findings

Based on the analyses of individual patients' changes in BPD Scale scores, anchored by changes in their response to the PGA of symptom severity, a 20-point change is recommended as the minimum meaningful change threshold for defining a responder. This threshold estimation used the "1-category improvement" PGA group as the target anchor, which is a significantly separated from the "no change" group with respect to the mean change on the BPD Scale. The choice of "1-category improvement" as the target anchor is supported by the majority (17/25, 68%) of the interviewed patients in the exit interview study reporting that a 1-category improvement on the PGA of symptom severity is meaningful to them. The responder threshold of a 20-point change

on the BPD Scale score is larger than what the majority of patients in the exit interview study reported to be meaningful to them, ie, an improvement between 5- to 15-points.

In summary, based on the triangulation of findings from the anchor-based analyses supported by patients' feed-back during exit interviews, a 20-point change in the BPD Scale is proposed as the responder threshold for change in BPD Scale.

4.6. References

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APPENDIX 5. ESTIMATION OF RESPONDER THRESHOLD FOR THE UFS-QOL REVISED ACTIVITIES SCALE

5.1. Approach to Estimating the Responder Threshold of the Revised Activities Scale

The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) Revised Activities Scale includes five of the seven most relevant items pertaining to physical and social activities (Coyne 2018). These are:

During the previous 3 months, how often have your symptoms related to uterine fibroids:

- Interfered with your physical activities?
- Made you decrease the amount of time you spent on exercise or other physical activities?
- Made you feel that it was difficult to carry out your usual activities?
- Interfered with your social activities?
- Caused you to plan activities more carefully?

Response options include:

- None of the time;
- A little of the time;
- Some of the time;
- Most of the time;
- All of the time.

The summary score of the five items ranges from 0 to 100, where a lower score indicates a higher ability to do activities (ie, lower score = good) and a higher score indicates a lower ability to do activities.

Change from Baseline to Week 24 in the Revised Activities Scale score is a secondary endpoint of the pivotal studies (MVT-601-3001 and MVT-601-3002) to evaluate the treatment benefit of relugolix + E2/NETA (Group A) compared with placebo (Group C). Additionally, a responder analysis will be performed between the two groups with respect to the proportion of patients who have achieved a meaningful reduction from Baseline to Week 24 in the Revised Activities Scale.

The approach used to derive the responder threshold for improvement in the Revised Activities Scale is similar to that used for the Bleeding and Pelvic Discomfort (BPD) scale (see details in Appendix 4).

This appendix briefly describes the quantitative and supportive qualitative methods and summarizes the respective analysis results.

The meaningful change threshold is the smallest reduction in the Revised Activities Scale score that is considered meaningful by patients (Cohen, 1988; Crosby, 2003; Revicki, 2008; Wyrwich, 2013; Cappelleri, 2014; Coon, 2018). The magnitude of a meaningful change threshold depends

on the magnitude of the correlation between the change in the Revised Activities Scale score and change in anchor (ie, the Patient Global Assessment [PGA] for function anchor) as well as the variability of change on the Revised Activities Scale by improvement categories on the PGA of symptoms (described in Section 5.2.2). Several anchor-based methods will be used; however, the primary analysis will be a measure of central tendency for each improvement category (see Section 5.2.3). Anchor-based methods will use data collected on:

- The UFS-QoL Revised Activities Scale score at Baseline and Week 24; and
- The PGA of function score at Baseline and Week 24.

Results from the anchor-based analyses will be supported by qualitative data collected in a patient interview study (MVT-601-037), a substudy of the phase 3 trials, in which patients from selected sites in the United States (US) provided feedback on what they considered to be a meaningful change on the Revised Activities Scale and the PGA of function (described in Section 5.4).

5.2. Statistical Analysis Plan for Estimation of the Responder Threshold

5.2.1. Anchor and Its Correlation with UFS-QoL Endpoint

The PGA of function uses a five-point verbal rating scale and asks the patient:

> How much were your usual activities limited by uterine fibroid symptoms such as heavy bleeding over the last 4 weeks?

Response options include:

- No limitation at all
- Mild limitation
- Moderate limitation
- Quite a bit of limitation
- Extreme limitation

The categorical change from Baseline to Week 24 in PGA of function score will be derived, leading to nine possible outcomes ranging from +4 (denoting worsening) to -4 (denoting improvement). The change in PGA of function at Week 24 will be used as the anchor (see Table 5.2-1).

5.2.2. Target Anchor Category

The target anchor category is the anchor category that represents the minimum meaningful change and is used as the starting point to identify potential candidates for a meaningful change threshold. For the two pivotal studies, the target anchor category will be a one-point category improvement on the PGA of function (see Table 5.2-1), as this is typically considered as a minimal clinical important difference on a five-point Likert scale.

Table 5.2-1: Change in PGA as Anchor

Anchor	Anchor Change Category	Potential Target Anchor Change Category (To Be Used for Estimation of Meaningful Change Threshold)
Change in PGA of function	-4, -3, -2, -1 (improvement), 0 (same), +1, +2, +3, +4 (worsening)	-1-category change (improvement)

Abbreviations: PGA = patient global assessment.

5.2.3. Anchor-Based Methods

To determine the meaningful change threshold for the reduction in UFS-QoL Revised Activities Scale score, the anchor-based analyses described below will be performed.

The category (or point) change in PGA of function score will be used as the anchor to classify patients into response groups, depending on their level of change in the Revised Activities Scale from Baseline to Week 24 (see Table 5.2-1). Uncollapsed, categorical change on the PGA will range from +4 to -4. Collapsed, categorical change will be considered based on the distribution of change categories on the PGA of function. Usually, the collapsing occurs on the tails with extreme worsening (+4) or improvement (-4).

Among the anchor-based analyses described below, the within-group analysis will be primary and other analyses (including between-group analysis) are supportive.

5.2.3.1. Correlation with Anchor

Correlation between the categorical change on the PGA of function score and the change in the Revised Activities Scale score will be evaluated at Week 24, using blinded pooled data from the first third of the enrolled patients from the two pivotal studies who had completed Week 24 visits and had the corresponding PGA of function data available (denoted as the "threshold determination analysis set"). Polyserial correlation coefficient will be used with a criteria value of > 0.30 indicating meaningful correlation (Cohen, 1988; Crosby, 2003; Revicki, 2008; Cappelleri, 2014; Coon, 2018).

5.2.3.2. Within-Group Meaningful Change

The magnitude of change from Baseline to Week 24 in Revised Activities Scale score will be calculated within each anchor category group. Changes in Revised Activities Scale scores are negative for reduced ability to do activities (indicating a worse outcome) and positive for increased ability to do activities (indicating a better outcome).

Descriptive statistics (*n*, mean change, median change, 25th and 75th percentiles, standard deviation [SD], confidence interval [CI], and standardized effect size [SES]) will be reported for the changes in Revised Activities Scale scores by anchor category. The SES will be calculated for each level of anchor category group by dividing the mean change score of Revised Activities Scale from Baseline by the Baseline SD of the anchor category group. The impact of treatment will be judged based on Cohen's recommendations (1988): small change (SES = 0.20),

moderate change (SES = 0.50), and large change (SES = 0.80). Significance associated within-patient change will be evaluated using paired t-tests on the change in Revised Activities Scale score separately for each level of improvement on the anchor.

5.2.3.3. Supportive Analysis of Between Group Meaningful Change Using Analysis of Variance

Analysis of variance (ANOVA) will be used to determine whether a difference in mean change scores from Baseline to Week 24 on the Revised Activities Scale exists between the categorical change groups (or the collapsed groups, as appropriate). Providing there is a significant change in Revised Activities Scale scores between the (collapsed) anchor groups, the between-group differences will be explored. Any anchor group with at least 15 patients will be included in this analysis. An anchor group with < 15 patients (usually occurring on the tails with extreme worsening [+4] or improvement [-4]) will be collapsed with its adjacent group as appropriate. Comparison of the anchor groups of interest between the target anchor ("-1 change" category) and "0 change" category will be performed using a t-test. A statistically significant difference on the Revised Activities Scale change scores corresponding to a 1-category change on the PGA of function can be used as supportive information for estimating the meaningful change threshold.

5.2.3.4. Visualizing Cumulative Distribution Function and Probability Distribution Function Plots by Anchor Category Group

Anchor-based meaningful change will also be evaluated using cumulative distribution function (CDF) plots utilizing the Kernel smoothing for all anchor category groups, based on cumulative change in the Revised Activities Scale scores for all available changes from Baseline to Week 24. Specifically, the CDF plot for each anchor category displays the probability (presented on y-axis) of patients who have achieved a given absolute change of X or less in the Revised Activities Scale score from Baseline to Week 24 for each point change along the range of possible absolute changes (from -100 [maximum reduction] to 0 [no change] to 100 [maximum increase]) expressed on the x-axis.

Similarly, the smooth probability density function (PDF) will also be plotted for each anchor category group over the range of absolute changes in the Revised Activities Scale scores. These probabilities are plotted on the y-axis with the Revised Activities Scale change score on the x-axis.

The CDF and PDF curves are delineated by anchor improvement category (from -4 to +4) displaying the center and separation between the curve for the target anchor group and the curve for the group reporting no change on PGA of function. It is expected that the CDF curves will not cross between the change category groups (eg, monotonic increase from no change to slightly improved and moderately improved).

5.2.4. Determining a Meaningful Change Threshold Using Totality-of-Evidence Approach

The meaningful change threshold will be determined using the totality of evidence from the results of above quantitative anchor-based analyses; results from the interview study (MVT-601-037) will be used as supportive evidence.

The results of these analyses and proposed thresholds will be included into the Patient-Reported Outcome dossier to be submitted at time of filing.

5.3. Results from Anchor-Based Analyses

5.3.1. Correlation of Change in Revised Activities Scale Score with PGA of Function

Meaningful change for the UFS-QoL Revised Activities Scale was derived based on anchor-based methods, supported by CDF and PDF curves. To assess the suitability of the selected anchor, PGA of function, a polyserial correlation was calculated between change on the PGA from Baseline to Week 24 and the change from Baseline to Week 24 on the Revised Activities Scale. The change in the PGA was moderately negatively correlated (r = -0.60) with the change on the Revised Activities Scale (Table 5.3-1). Given that the PGA of function is less complex than the Revised Activities Scale, this result indicates that the PGA of function is a suitable anchor for the Revised Activities Scale.

Table 5.3-1: Summary of Change from Baseline to Week 24 in UFS-QoL Revised Activities Scale by PGA of Function Change Category (mITT Population)

PGA of Function Change Category	N = 254	Change in Revised Activities					Correlation between PGA Change and Revised Activities Change[a]
		Mean (SD)	Median	95% CI	p-value[b]	SES[c]	
4-category deterioration (+4)	**2**	5.00 (7.07)	5	-58.53,68.53	0.500	0.28	-0.60
3-category deteriorations (+3)	**2**	0	0	-	-	0.00	
2-category deteriorations (+2)	5	7.00 (22.80)	0	-21.31,35.31	0.5302	0.61	
1-category deteriorations (+1)	**22**	-1.59 (23.82)	-5	-12.15,8.97	0.7572	-0.06	
0 Category deteriorations (0)	71	11.55 (28.51)	5	4.80,**18.30**	0.0011	0.38	
1-category improvement (-1)	53	**27.92** (25.65)	**20**	**20.85**,35.00	< 0.0001	1.06	
2-category improvement (-2)	**51**	51.86 (27.60)	60	44.10,59.63	< 0.0001	2.17	
3-category improvement (-3)	**35**	56.81 (27.49)	57.50	47.50,66.11	< 0.0001	2.91	
4-category improvement (-4)	13	60.77 (31.55)	70	41.71, 79.83	< 0.0001	4.40	

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; PGA = patient global assessment; SD = standard deviation; SES = standardized effect size.
mITT is used to calculate change from Baseline score at Week 24 and includes patients from the mITT population who have available change from Baseline data at Week 24.

[a] Polyserial correlation coefficient between change in Revised Activities Scale and change in PGA of function.

[b] The p-value for each individual change group is derived from a paired (within-sample) t-test assessing the difference over time.

[c] SES calculated as the mean divided by the SD of Baseline. SES is judged as small = 0.2, moderate = 0.5, and large = 0.8 (Cohen 1988).

5.3.2. Improvement on Revised Activities Scale by PGA Change Category

Uncollapsed changes on the PGA of function were used to determine minimal meaningful improvement on the Revised Activities Scale (Table 5.3-1). Improvement on the Revised Activities Scale increased monotonically for all the categories from "no change (0)" to "1-category improvement (-1)" to "2-category improvement (-2)" with non-overlapping 95% CIs for mean change of the three groups. Table 5.3-2 shows that a one category improvement (-1) is associated with a 27.92-point mean improvement in the Revised Activities Scale score at Week 24 compared to Baseline, with a 95% CI [20.85, 35.00], a large SES = 1.06, and a median improvement of 20 points.

Table 5.3-2 highlights that the difference between the "1-category improvement" and the "no change" groups (mean =11.55 with a 95% CI of [4.80, 18.30]) was statistically significant (p = 0.0013) with a moderate SES = 0.54, which reasonably supports the notion that patients interpreted these change categories as distinct.

Table 5.3-2: Summary of Change from Baseline to Week 24 in Revised Activities Scale Between Target Anchor (-1) and No change (0) in PGA of Function (mITT Population)

Anchor	Categorical Change	N	Mean Change from BL	SD	95% CI	p-value[a]	Baseline SD	SES
PGA	1-category improvement (-1)	53	**27.92**	**25.65**	**20.85, 35.0**			
	No change (0)	71	**11.55**	**28.51**	**4.80, 18.30**			
	Difference		**16.38**	**27.33**	**6.55, 26.20**	0.0013		0.54[b]
								0.57[c]

[a] The p-value is based on t-test for difference in mean change in BPD score between the 2 anchor groups (-1 and 0) from the ANOVA.

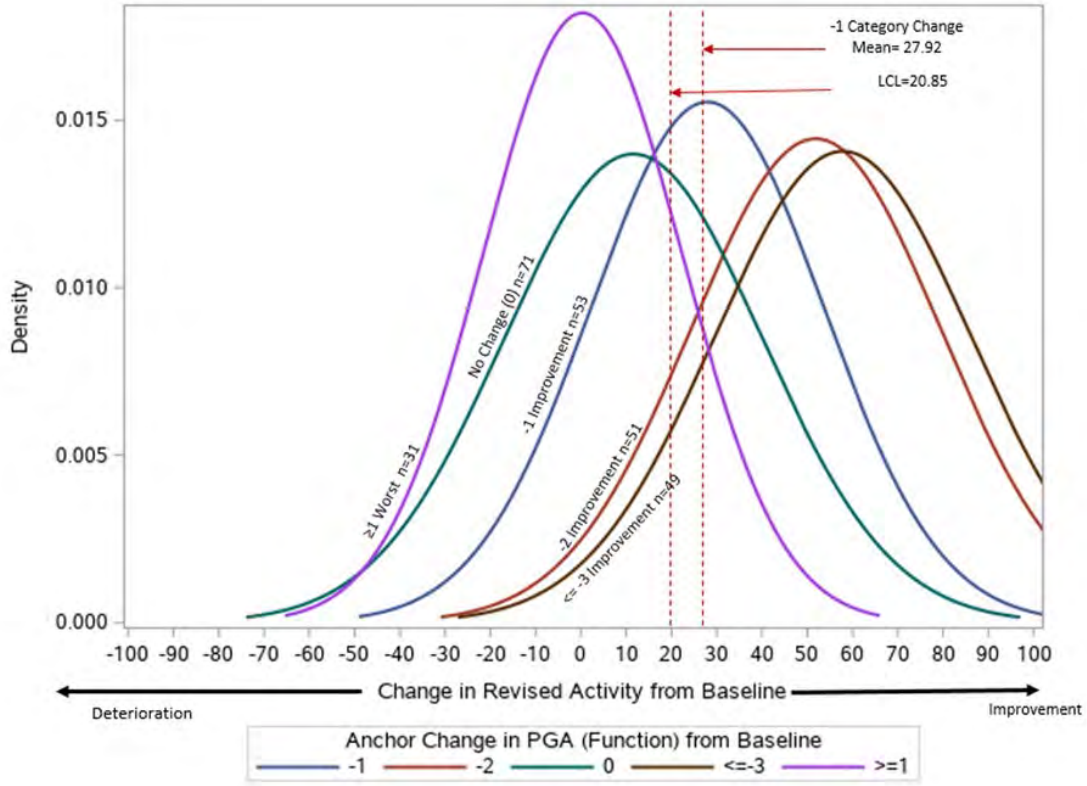
[b] SES calculated as the mean difference divided by the standard deviation of Baseline for no change group. They are judged as small=0.2, moderate=0.5 and large=0.8 (Cohen, 1988).

[c] SES calculated as the mean difference divided by the standard deviation of Baseline for pooled from all categories (Glass, 1976).

That patients were able to distinguish between the PGA "1-category improvement" and the 'no change" group is further supported by the nonoverlapping CIs (in Table 5.3-2) for the respective UFS-QoL Revised Activities Scale scores and as illustrated by the separation between the CDF curves presented in Figure 5.3-1. Since statistically significant differences existed in patient responses on the Revised Activities Scale between the "1-category improvement (-1) " option and the "no change" and the "2-category improvement (-2)" groups, a 1-category improvement on the PGA was considered a meaningful target anchor category for assessing the responder threshold on the Revised Activities Scale. Although a two-category improvement could have been considered for deriving the meaningful change threshold, such a threshold would not qualify as being the *minimum* threshold possible. The evidence (ie, the statistical difference between the1- and 2-category improvements and the fact that patients were able to distinguish between the two response options) supports using a 1-category improvement on the PGA of

function for estimating the minimum meaningful change threshold. This decision is also supported by qualitative evidence generated from the Exit Interview study (see Section 5.4).

Figure 5.3-1: PDF of the Change in UFS-QoL Revised Activities by PGA of Function Anchor Change Category (Collapsed)



Abbreviations: PGA = patient global assessment; LCL = lower confidence limit.

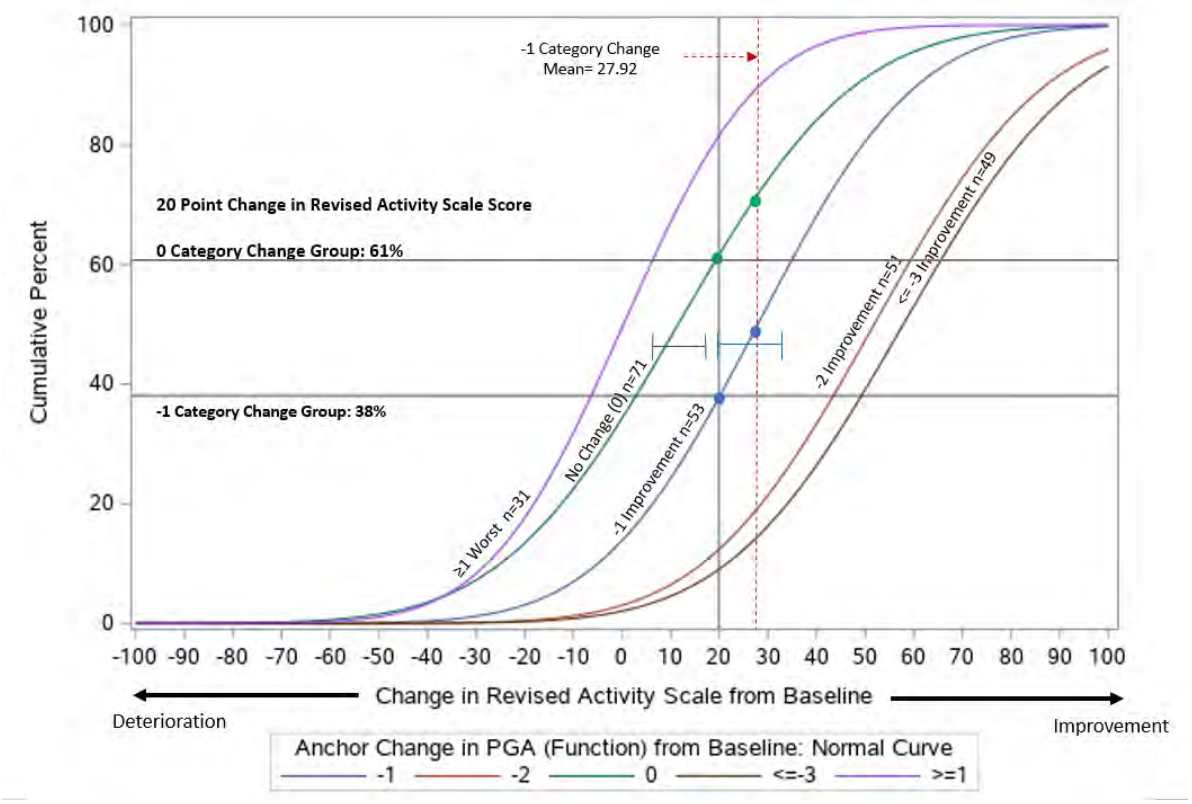
5.3.3. Estimation of Responder Threshold

Using the mean value for measuring improvement in the Revised Activities Scale would yield estimates that are conservative because expected values do not necessarily constitute a *minimum* meaningful change threshold for patients. That is, nearly half the patients stratified in the PGA "1-category improvement" who reported changes smaller than the mean on the Revised Activities Scale would be classified as nonresponders by using the mean as the threshold despite of their reporting "1-category improvement". A less conservative, though still plausible estimate for the minimal meaningful change threshold is the lower bound of the 95% CI for mean change in the "1-category improvement" group. Its use will result in a smaller proportion of patients being classified as nonresponders on the Revised Activities Scale than the expected value (ie, the mean). Similarly, one can also consider the median value since it is less influenced by outliers than either the mean or CI estimates.

According to the uncollapsed anchor-based analysis (Table 5.3-1), the median value for a "1-category improvement" is 20-points, while the lower bound 95% CI for this group is about 21-points (ie, a 21-point improvement on the revised activities between Baseline and Week 24). Given the large discrepancy between the mean and median values suggests that outliers were present in the data; hence, the median value is recommended as a potential minimum change threshold.

Examination of the CDF curves for the potential minimum meaningful threshold value of 20 points on the Revised Activities Scale allows one to estimate the cumulative percent of patients that would experience the improvement. As illustrated in Figure 5.3-2, approximately 38% of the "no change" group and 61% of the "1-category improvement" group experienced at least a 20-point improvement (eg, approximately 62% of the "no change" group and 39% of the "1-category improvement" group experienced less than a 20-point improvement to the left) on the Revised Activities Scale by Week 24.

Figure 5.3-2: Cumulative Distribution Function of Change at Week 24in UFS-QoL Revised Activities Scale Score by PGA Anchor Change Category (Collapsed)

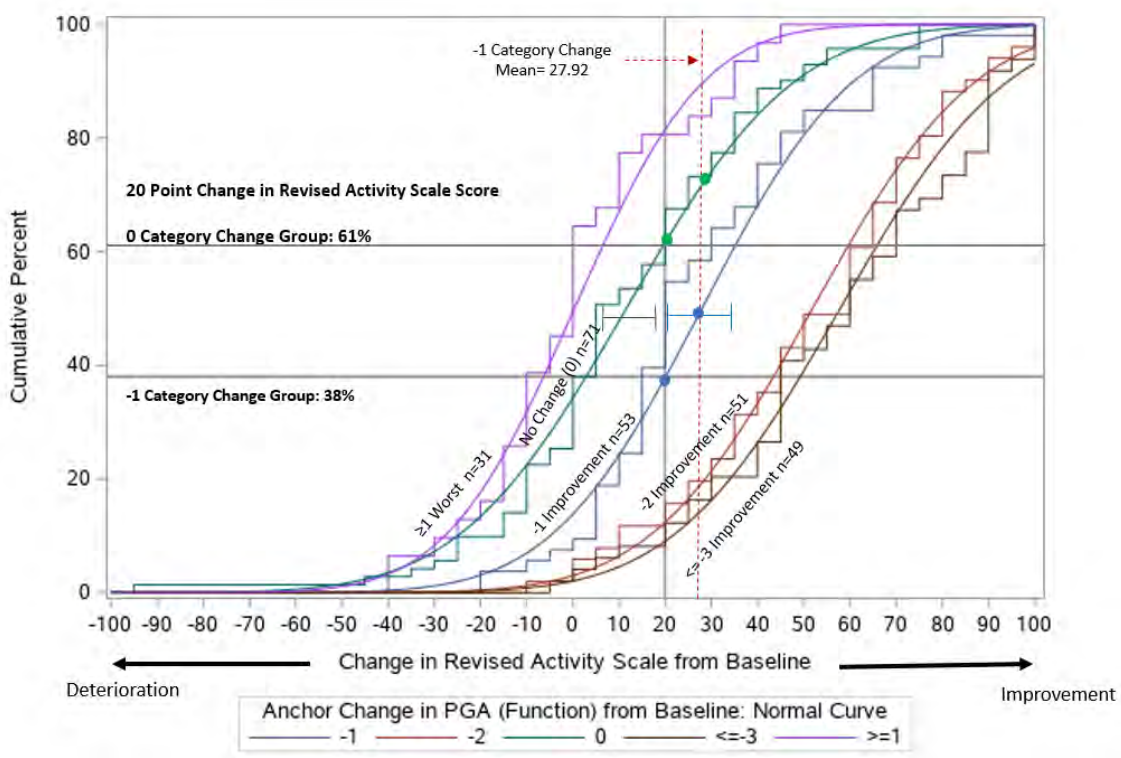


Abbreviations: PGA = patient global assessment.

As supportive information, the empirical CDFs with step-curves (reflecting the discrete nature of the revised activities scores) are provided (Figure 5.3-3), indicating that smooth curves are

reasonably close to the empirical CDFs. Examination of the PDF curves presented in Figure 5.3-1 indicates that the dispersion is roughly the same for the options between "> -3-category improvement" and "no change."

Figure 5.3-3: Empirical Cumulative Distribution Function of Change at Week 24 in UFS-QoL Revised Activities Scale Score by PGA Anchor Change Category (Collapsed)



Abbreviations: PGA = patient global assessment.

5.4. Exit Interview Study Synthesis

5.4.1 Objectives

The objectives of the exit interviews were: 1) to provide qualitative evidence to understand meaningful change for patients following clinical intervention and 2) to elicit data on what patients consider to be a minimum meaningful improvement on different patient-reported outcomes (PROs), including:

- The UFS-QoL Revised Activities Scale;
- The PGA of function.

These objectives were achieved through conducting web/Internet-based video or telephone interviews with English-speaking patients in the US within 3 to 14 days after their Week 24 visit

of either ongoing phase 3 clinical study (MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]).

Minimum meaningful improvements on other PROs were also explored as part of the exit interview study; results of the respective exercises will be included in the full report for this exit interview study.

5.4.2 Methodology – Qualitative Interviews

The exit interviews were conducted via a web/Internet-based video platform (Doxy.me [https://doxy.me/]) or via telephone by trained and experienced Endpoint Outcomes interviewers.

If a patient did not improve by at least 1 point from Baseline Day 1 to Week 24 based on her PGA of function, meaningful change exercises were not conducted for the PGA of function and the UFS-QoL Revised Activities Scale. An improvement on the PGA of function was required so that patients could provide contextually relevant feedback related to positive changes as they would have experienced an improvement throughout the trial. Table 5.4-1 summarizes the measures/scales of interest, the type of data that was used in the respective meaningful change exercises, and the criteria that must have been met in order for the patient to participate in the respective meaningful change exercise.

Table 5.4-1: Overview of Procedures for Meaningful Change Exercises

Measure/Scale	Type of Data Used	Criteria That Must Have Been Met in Order to Conduct the Respective Meaningful Change Exercise
UFS-QoL Revised Activities Scale (calculated)	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) Baseline Day 1 response	Improvement on PGA of function from Baseline Day 1 to Week 24
PGA (for function)	MVT-601-3001 (LIBERTY 1) or MVT-601-3002 (LIBERTY 2) responses (Baseline Day 1 and Week 24)	Improvement on PGA of function from Baseline Day 1 to Week 24

Abbreviations: PGA = patient global assessment; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.

For the UFS-QOL Revised Activities Scale, only patients' clinical study (ie, MVT-601-3001 [LIBERTY 1] or MVT-601-3002 [LIBERTY 2]) Baseline Day 1 data were used during interviews; the meaningful change discussions were hypothetical, as Week 24 data were not made available to Endpoint Outcomes.[4] For the UFS-QoL Revised Activities Scale, patients were provided with both their Baseline item-level scores and the summary score calculated based on the five items in the scale. Patients were also given a copy of the five items that comprise the UFS-QoL Revised Activities Scale for reference during the meaningful change exercise. Patients were then presented with pre-specified point change increments (ie, 10 points) and asked whether those changes reflected a meaningful improvement. If a patient indicated that a 10-point

[4] For secondary endpoint data, only Baseline responses were shared with Endpoint Outcomes.

increment change would be meaningful, she was asked if an increment 5 points fewer would still be meaningful. Using a stepwise approach, interviewers then moved along the scale to identify the point at which minimum meaningful improvement was achieved for the respective patient.

For the PGA of function, patients were presented with their clinical study scores at Baseline Day 1 and Week 24 and were asked if the change was meaningful. Next, patients were presented with a series of hypothetical point changes (ie, more change if the change was not meaningful or less change if the change was meaningful, as warranted) and asked if those would be meaningful. This process continued until the minimum meaningful change on the PGA of function for that patient was identified.

Audio-recordings of the interviews were transcribed verbatim and anonymized by removing identifying information such as names and places. Each transcript was considered a unit of analysis, and data from all transcripts were aggregated following coding. An initial coding scheme was developed based on the semi-structured interview guide and research objectives. The coding scheme was applied and operationalized using Atlas.ti version 8.2.30 (Atlas.ti GmbH, Berlin), a software program designed specifically for qualitative data analysis. Specifically, codes were applied to selected text within each transcript and then queried for frequency across transcripts. Frequencies of patients' interview responses (eg, minimum meaningful change responses) are reported. Minimum meaningful point change medians and ranges were calculated in Excel. As the sample size for the study was small and to reduce the influence of potential outliers, the median is the preferred measure of central tendency reported.

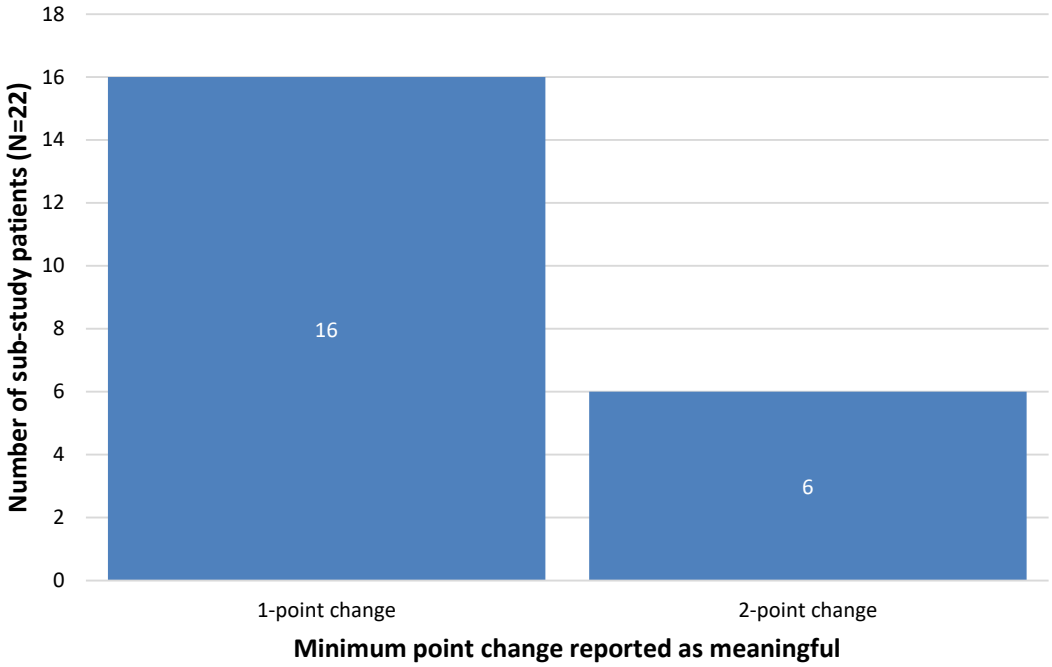
5.4.3 Results

5.4.3.1 PGA of Function[5]

Twenty-two patients improved from Baseline Day 1 to Week 24 on the PGA of function and participated in the PGA of function meaningful change exercise. The demographic characteristics of the 22 patients who completed the PGA of function closely match that of the entire substudy sample as the sample was mostly PPD (n = PPD PPD (n = PPD had completed at least some college or higher (n = 19, 86.4%), and had an average age of approximately 44 years. The median minimum point change considered to be a meaningful improvement was 1 point (n = 22, range = 1-2); the most frequently reported minimum meaningful improvement reported by patients was a 1-point change (n = 16, 72.7%) (Figure 5.4-1).

[5] The PGA of function asks: How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? Response options include: No limitation at all, mild limitation, moderate limitation, quite a bit of limitation, and extreme limitation.

Figure 5.4-1: Meaningful Change Estimation: Results of the PGA (for Function)



5.4.3.1 UFS-QoL Revised Activities Subscale[6]

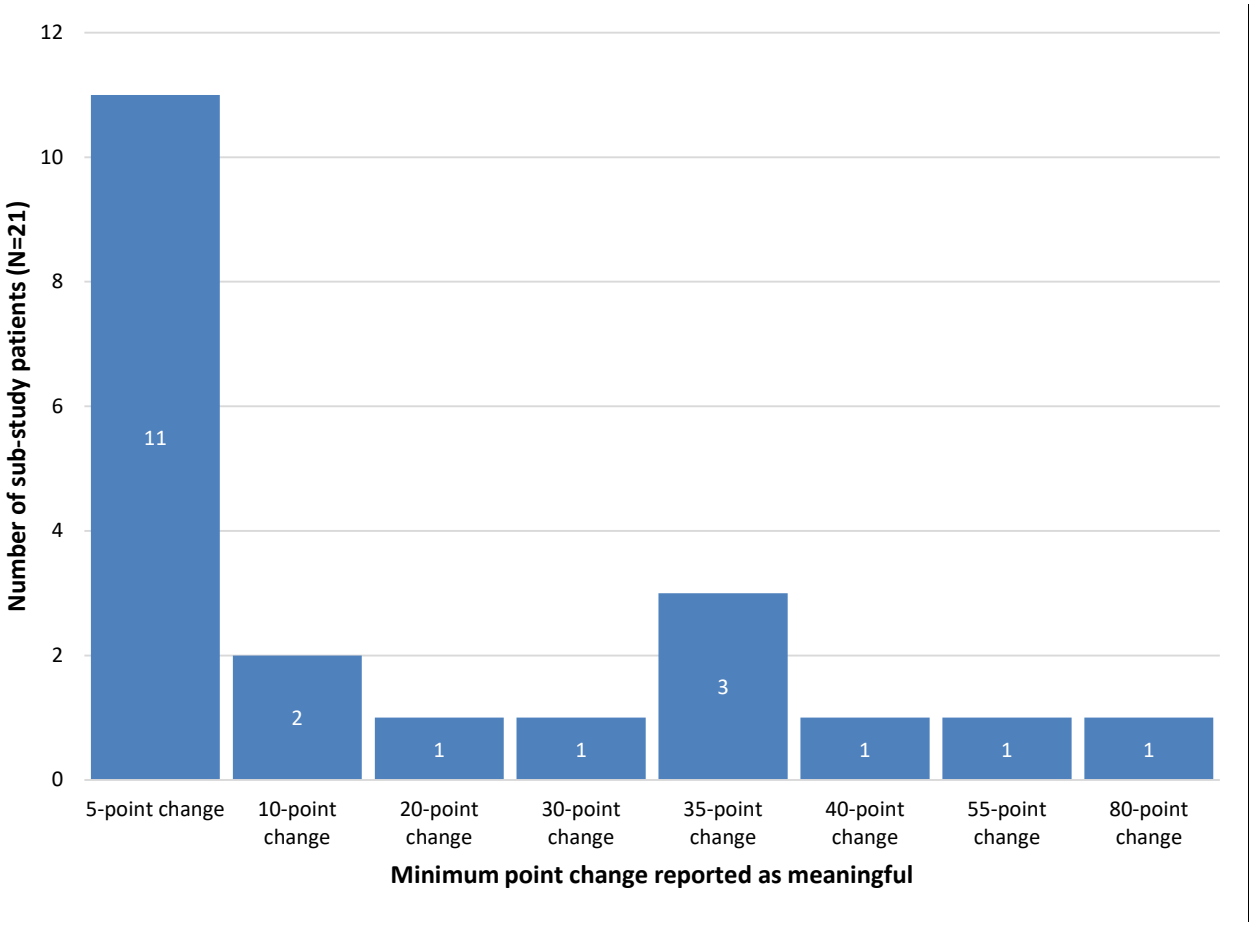
Twenty-two patients improved from Baseline Day 1 to Week 24 on the PGA of function and participated in the UFS-QoL revised activities subscale meaningful change exercise. Data for 21 patients were included in the analysis as one patient provided meaningful change exercise information that was not informative and therefore was excluded from the analysis.[7] The demographic characteristics of the 21 patients who completed the UFS-QoL Revised Activities Scale closely match that of the entire substudy sample as the sample was mostly PPD (n = PPD (n = PPD had completed at least some college or higher (n = 19, 90.5%), and had an average age of approximately 44 years.

[6] The UFS-QoL revised activities subscale includes five items, which ask: During the previous 3 months, how often have your symptoms related to uterine fibroids … 11) interfered with your physical activities; 13) made you decrease the amount of time you spent on exercise or other physical activities; 19) made you feel it was difficult to carry out your usual activities; 20) interfered with your social activities; and 27) made you plan activities more carefully. Response options include 1) None of the time, 2) A little of the time, 3) Some of the time, 4) Most of the time, and 5) All of the time. The score range for the subscale is 0-100. A higher score on the revised activities subscale indicates a lower interference in activities while a lower score on the subscale indicates a higher interference in activities.

[7] This patient was unwilling to describe the minimum point change needed for meaningful improvement for the UFS-QoL revised activity subscale.

The median minimum point change considered to be a meaningful improvement was 5 points (n = 21, range = 5-80); the most frequently reported minimum meaningful improvement reported by patients was a 5-point change (n = 11, 52.4%) (Figure 5.4-2).

Figure 5.4-2: Meaningful Change Estimation: Results of the UFS-QoL Revised Activities Subscale



5.5. Determination of Responder Threshold via Triangulation of Findings

Based on the analyses of individual patient's change in Revised Activities Scale scores anchored by change in their response to the PGA of function, a 20-point change is recommended as the minimum meaningful change threshold for defining a responder. This threshold estimation used the "1-category improvement" PGA group as the target anchor, which is significantly separated from the "no change" group with respect to the mean change on the Revised Activities Scale. The choice of "1-category improvement" as the target anchor is supported by the majority (16/22, 73%) of the interviewed patients in the exit interview study reporting that a 1-category improvement on the PGA of function is meaningful to them. The responder threshold of a 20-point change on the Revised Activities Scale score is larger than what the majority of patients in the exit interview study reported to be meaningful to them (ie, improvements of 5 points [11/21] and 10 points [2/21]).

In summary, based on the triangulation of findings from the anchor-based analyses supported by patients' feedback during exit interviews, a 20-point change in the Revised Activities Scale is proposed as the responder threshold for change in Revised Activities Scale.

5.6. References

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