Supplementary Appendix

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

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Supplementary Methods

Selection of Study Population

Table S1. Eligibility Criteria.

Inclusion Criteria
A woman was eligible for randomization and enrollment in this study only if all of the following inclusion criteria applied and were met at the time of the baseline Day 1 visit, unless otherwise specified. 1. Had voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures; 2. Was a premenopausal female 18 to 50 years of age (inclusive) on the day of signing and dating the informed consent form; 3. Had 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 three months prior to the screening 1 visit; 4. Had a diagnosis of uterine fibroids that was confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid had to 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: Once the transvaginal ultrasound was completed, a transabdominal ultrasound could have been performed if the uterus could not be adequately imaged on transvaginal ultrasound (i.e., because of enlarged size). Note: Saline or gel contrast was not required but could have been performed to demonstrate fibroids that met the criterion for inclusion if these were not adequately visualized with transvaginal ultrasound alone. 5. Had heavy menstrual bleeding associated with uterine fibroids, as evidenced by a menstrual blood loss volume of ≥160 ml during 1 cycle or ≥80 ml per cycle for two menstrual cycles, as measured by the alkaline hematin method during the screening period; 6. Patient did not expect to undergo gynecological surgery or ablation procedures for uterine fibroids within the six months following enrollment; 7. Had a negative urine pregnancy test at the Screening 1, Screening 3, and baseline Day 1 visits; 8. Agreed to use contraception during the study and for 30 days following the last dose of study drug. Specifically agreed to use non-hormonal contraception consistently during the screening period and the randomized treatment period and either non-hormonal or oral contraceptives after return of menses following treatment discontinuation. However, the patient was not required to use specified non-hormonal contraception if the following applied: a. Had sexual partner(s) who were vasectomized at least six months prior to the screening period; b. Had a bilateral tubal occlusion (including ligation and blockage methods, such as Essure™), at least four months prior to the first screening visit (patients with Essure had to have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome," in the investigator's opinion); c. Was not sexually active with men; periodic sexual relationship(s) with men required the use

of non-hormonal contraception.

9. Had 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 were detected on biopsy but were either not evident on ultrasound or <2 cm were eligible;

10. If ≥39 years of age at the time of the baseline Day 1 visit, had a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within six months prior to the screening period.

Exclusion Criteria

1. Had transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could have been responsible for or contributed to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥2 cm, large simple ovarian cyst >4.0 cm, endometrioma(s) >4.0 cm, or any other clinical significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

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

2. Had known rapidly enlarging uterine fibroids, in the opinion of the investigator;
3. Had 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 six months prior to the screening 1 visit;
4. Had a weight that exceeded the weight limit of the dual-energy x-ray absorptiometry scanner or had a condition that precluded an adequate dual-energy x-ray absorptiometry measurement at the lumbar spine and proximal femur (e.g., bilateral hip replacement or spinal hardware in the lumbar spine);
5. Had a baseline bone mineral density z-score <-2.0 at the spine, total hip, or femoral neck;
6. Had a history of or currently had osteoporosis, or other metabolic disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures were allowed). Patients whose hyperparathyroidism or hyperthyroidism had been successfully treated or whose hyperprolactinemia had been successfully treated and/or who met bone mineral density eligibility criteria for the study were allowed;
7. Had 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 glucocorticoids were permitted without restriction.

9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Had any contraindication to treatment with estradiol and norethindrone acetate, including the following:
    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 or 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. Had jaundice or known current active liver disease from any cause, including hepatitis A, hepatitis B, or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid);
12. Had any of the following cervical pathology: high-grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia were allowed in the study if high-risk human papilloma virus testing was negative or if deoxyribonucleic acid testing for human papilloma virus 16 and 18 was negative;
13. Had any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin <8.0 g per deciliter (patients with screening hemoglobin results <8 g per deciliter may have been prescribed iron supplements and had their hemoglobin levels retested prior to the baseline Day 1 visit);
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) >1.5 times ULN on clinical laboratory testing at either the screening 1 or screening 2 visit (or >2.0 times ULN if secondary to Gilbert syndrome or patter consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate <60 ml/min/m^2 using the Modification of Diet and Renal Disease method;
    d. Hypocalcemia (< lower limit of normal [LLN] or hypocalcemia (>ULN);
    e. Hypophosphatemia (<LLN) or hyperphosphatemia (>ULN);
14. Had clinically significant cardiovascular disease, including the following:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (i.e., ≥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 permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥120 beats per minute);
    e. QT interval by the Fridericia correction (QTcF) of >470 msec on the screening visit or baseline Day 1 electrocardiogram;
    f. Hypotension, as indicated by a systolic blood pressure <84 mmHg on two 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 two repeat measures at least 15 minutes apart at any screening visit or baseline Day 1 visit;

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

15. Had been a participant in an investigational drug or device study within the one month prior to the screening 1 visit;
16. Had a history of clinically significant condition(s), including but not limited to the following:

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

    b. History of malignancy within the past five years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cleared 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, based on the Diagnostic and Statistical Manual of Mental Disorders-5 criteria who had been unstable or not well controlled based on the investigator's or mental health professional's judgment or whose history or stability could not be ascertained, or whose psychiatric drug regimen had changed during the three months prior to screening or was expected to change during the study should not have been enrolled;

    d. Had a systemic autoimmune disease (e.g., 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 was permitted;

17. Was pregnant or lactating, or intended to become pregnant during the study period through one month after the last dose of study drug or intended to donate ova during the study period or within two months after the last dose of study drug;
18. Was using any prohibited medications;
19. Had a contraindication or history of sensitivity to any of the study treatments or components thereof; or had a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicated study participation;
20. Had a prior (within one year of screening 1 visit) or current history of drug or alcohol abuse disorder according the Diagnostic and Statistical Manual of Mental Disorders-5 (all patients had to be questioned about their drug and alcohol use and this should have been documented in the electronic case report form);
21. Had participated in a previous clinical study that included the use of relugolix;
22. Was an immediate family member, study site employee, or was in a dependent relationship with a study site employee who was involved in the conduct of the study (e.g., spouse, parent, child, or sibling);
23. Was inappropriate for participation in this study because of conditions that may have interfered with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, subinvestigator, or medical monitor;
24. Had received a blood transfusion within eight weeks prior to the screening 1 visit or during the screening period.

Study Objectives and End Points

The objectives and end points of the study are listed in the following table. All end points were prespecified in the statistical analysis plan, which was finalized prior to database lock and unblinding of the data. These analyses differ from what was originally included in the protocol, as described in the statistical analysis plan.

Table S2. Study Objectives and End Points.

Objective(s)	End Point(s)
Primary Efficacy	
To determine the benefit of relugolix 40 mg once a day co-administered with estradiol 1 mg and norethindrone acetate 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids	Proportion of women in the relugolix combination therapy group versus the placebo group who achieve an MBL 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
Key Secondary Efficacy (Alpha-Protected for Hierarchical Hypothesis Testing — Relugolix Combination Therapy 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 menstrual blood loss 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 per deciliter at baseline who achieve an increase of >2 g per deciliter from baseline at week 24
Pain associated with uterine fibroids	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
Uterine fibroid volume	Percent change from baseline to week 24 in volume of the largest uterine fibroid at baseline
Uterine volume	Percent change from baseline to week 24 in uterine volume

Objective(s)	End Point(s)
Other Secondary Efficacy (Not for Hierarchical Hypothesis Testing)*	
To determine the benefit of relugolix 40 mg once a day for 12 weeks followed by 12 weeks of relugolix 40 mg once a day co-administered with estradiol 1 mg and norethindrone acetate 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids	Proportion of women in the delayed relugolix combination therapy group versus the placebo group 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
Heavy menstrual bleeding associated with uterine fibroids	• Percent change from baseline to Weeks 4, 8, 12, 16, and 20 in menstrual blood loss volume • Change from baseline in menstrual blood loss volume by visit • Time to achieve an 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 • Proportion of women in the relugolix combination therapy group versus the placebo group who achieve an menstrual blood loss volume of <80 ml AND at least a 50% reduction from baseline menstrual blood loss 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 who with a hemoglobin concentration below the lower limit of normal at baseline who achieved an increase of ≥1 g per deciliter from baseline at week 24 • Change from baseline to week 24 in hemoglobin for women with a hemoglobin concentration ≤ 10.5 g per deciliter 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)	End Point(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	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 a day co-administered with either 12 or 24 weeks of estradiol 1 mg and norethindrone acetate 0.5 mg in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks	Treatment-emergent adverse events (hereafter referred to as 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 combination therapy group compared with the delayed relugolix combination therapy 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 combination therapy group compared with the delayed relugolix combination therapy group, as assessed by dual-energy x-ray absorptiometry
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 a day co-administered with either 12 or 24 weeks of estradiol 1 mg and norethindrone acetate 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 dual-energy x-ray absorptiometry

Objective(s)	End Point(s)
To determine the incidence of vasomotor symptoms with relugolix 40 mg once a day co-administered with either 12 or 24 weeks of estradiol 1 mg and norethindrone acetate 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 a day when co-administered with either 12 or 24 weeks of estradiol 1 mg and norethindrone acetate 0.5 mg	• Predose trough concentrations (C_τ) of relugolix, and NET and baseline-adjusted estradiol concentration • Absolute and changes from baseline to week 24 in predose concentrations of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone
Exploratory	
To determine the benefit of 24 weeks of relugolix 40 mg once a day co-administered with either 12 or 24 weeks of estradiol 1 mg and norethindrone acetate 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

EQ-5D-5L denotes EuroQoL five-dimensions questionnaire (five-level version), NRS, numerical rating scale; PGA, patient global assessment, and UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire.

* The secondary end points below were assessed comparing relugolix Group A to placebo Group C inferentially; relugolix Group A to relugolix Group B and relugolix Group B to placebo Group C descriptively, unless otherwise specified.

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Mixed-Effects Model for Imputing Missing Menstrual Blood Loss Volume Data

For the primary analysis, patients with missing menstrual blood loss volumes at week 24/end of treatment were identified per missing data handling rules. For imputing missing data for the primary analysis, a mixed-effects model approach was 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 menstrual blood loss volumes at multiple time points (Weeks 4, 8, 12, 16, 20 and 24) was fitted to predict percent change in menstrual blood loss volume from baseline (as a dependent variable) through the fixed-effects associated with covariates (i.e., stratification factors of baseline menstrual blood loss 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 was assumed for each patient.

See sample SAS codes below for illustration where PCHG_MBL is percent change in menstrual blood loss 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 combination therapy 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 menstrual blood loss 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 menstrual blood loss volume data, the fixed-effects were estimated and relationship of percent change in menstrual blood loss volume from baseline with the covariates was characterized by the fitted model. From the fitted model, the percent change in menstrual blood loss volume (whether missing or not) was predicted for each patient at each visit and in a particular stratum. The imputed menstrual blood loss volume was obtained by first multiplying the imputed percent change with the individual patient's baseline menstrual blood loss volume to the difference, and then adding the baseline menstrual blood loss volume to the difference.

The main reason for using percent change in menstrual blood loss volume over reported menstrual blood loss volume as a dependent variable in the mixed-effects model is that the percent change is part of the derivation of the primary end point. Secondly, the percent change is a normalized value adjusted for the baseline value and less influenced by baseline menstrual blood loss volume, and therefore it is a better metric to describe the relationship of menstrual blood loss 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 blood loss volumes identified at week 24/end of treatment, the predicted menstrual blood loss volumes at the corresponding week 24/end of treatment visit were used to determine responder status. For patients without the need for imputation, their responder status was derived according to the algorithms laid out in Table S3. This imputation approach is consistent with the definition of responder at week 24/end of treatment for the primary analysis.

Derivation of Responder Status at Week 24/End of Treatment and Missing Data Handling Rules

For the evaluation of primary end point, missing data handling rules were implemented for deriving responder status at week 24/end of treatment as described below. The following elements were checked: duration of treatment exposure; compliance with menstrual product collection against the daily electronic diary, as measured by their menstrual product return rate compliance with electronic diary entry, defined as the proportion of electronic diary entry days over the length (days) of menstrual product collection interval for week 24/end of treatment visit; and reasons for no menstrual product collection (as displayed in Table S3).

Patients with <4 weeks of treatment who withdrew from the study prematurely due to lack of efficacy or withdrew from the study prematurely to undergo surgical intervention for uterine fibroids were considered as non-responders.

All other patients had their responder status determined as follows:

- For patients with a menstrual product return rate of 100%, responder status was determined based on the observed menstrual blood loss volume;
- For patients who had incomplete menstrual product collection, with a menstrual product return rate of <100%, responder status was derived based on either imputed or observed menstrual blood loss volume;
  - Those with a menstrual blood loss volume ≥80 ml or <50% reduction from baseline were considered as non-responders;
  - Those with a menstrual blood loss volume <80 ml and ≥50% reduction from baseline were imputed for partial or complete missing menstrual blood loss volume.
- For patients who did not return a menstrual product collection, responder status was determined depending on the reason reported on the Feminine Product Collection eCase Report Form:
  - If the reason was reported as Amenorrhea, the last 35 days of treatment were used to derive responder status:
    - If the week 24/end of treatment interval was 35 days, then she was considered as a responder;
    - If the week 24/end of treatment interval was <35 days, the following supportive information was used to derive responder status:
      - If a patient reported amenorrhea at the visit prior to week 24/end of treatment, she was defined as a responder;
      - If a patient did not report amenorrhea at the visit prior to week 24/end of treatment, electronic diary data from the prior visit interval was reviewed to confirm whether the patient was amenorrheic for a total of 35 days.

- If the electronic diary from the previous interval confirmed amenorrhea, then the patient was considered as a responder;
- Otherwise, menstrual blood loss volume was imputed.

- If the reason was Other and the specification described spotting or negligible bleeding, responder status was defined as follows:
    - The patient was considered as a responder if it was supported by the electronic diary data: the electronic diary entry rate must have exceeded 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 electronic diary entries did not confirm spotting or negligible bleeding, but the patient had at least 8 weeks of menstrual blood loss volume data prior to the week 24/end of treatment visit, her missing menstrual blood loss volume was imputed to determine responder status. Eight weeks of menstrual blood loss volume data represented 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 menstrual blood loss volume data, she was considered as a non-responder;
- If the reason was any Other, the responder status was derived as follows:
    - If the patient had at least 8 weeks of menstrual blood loss volume data prior to the week 24/end of treatment visit, her missing menstrual blood loss volume was imputed and her responder status was based on the imputed menstrual blood loss volume.
    - If the patient had <8 weeks of menstrual blood loss volume data, she was considered as a non-responder.

Table S3. Derivation of Responder Status at Week 24/End of Treatment and Missing Data Handling Rules – for Primary Analysis.

Treatment Exposure	Menstrual Product Return Rate	Observed Menstrual Blood Loss Volume	Reason for No Menstrual Product Collection	Responder Status
<4 weeks	N/A	N/A	N/A	Imputed as non-responder
≥4 weeks	100% Menstrual Product Compliance	N/A	N/A	Based on the observed menstrual blood loss volume
	<100% Menstrual Product Compliance	Menstrual blood loss volume ≥80 ml or <50% reduction from baseline	N/A	Imputed as non-responder based on the observed menstrual blood loss volume
		Menstrual blood loss volume <80 ml and ≥50% reduction from baseline	N/A	Based on the imputed menstrual blood loss volume
	No Menstrual Product Collection	N/A	Reported "Amenorrhea"	Imputed as responder
			Reported "Spotting or negligible bleeding" and confirmed by eDiary*	Imputed as responder
			Reported "Spotting or negligible bleeding" although not confirmed by eDiary or any other reason, had at least 8 weeks of menstrual blood loss volume data	Based on the imputed menstrual blood loss volume
			The entries in the eDiary did not verify "Spotting or negligible bleeding" or any other reason and if had <8 weeks of menstrual blood loss volume data	Imputed as non-responders

eDiary denotes electronic diary, and N/A not available.

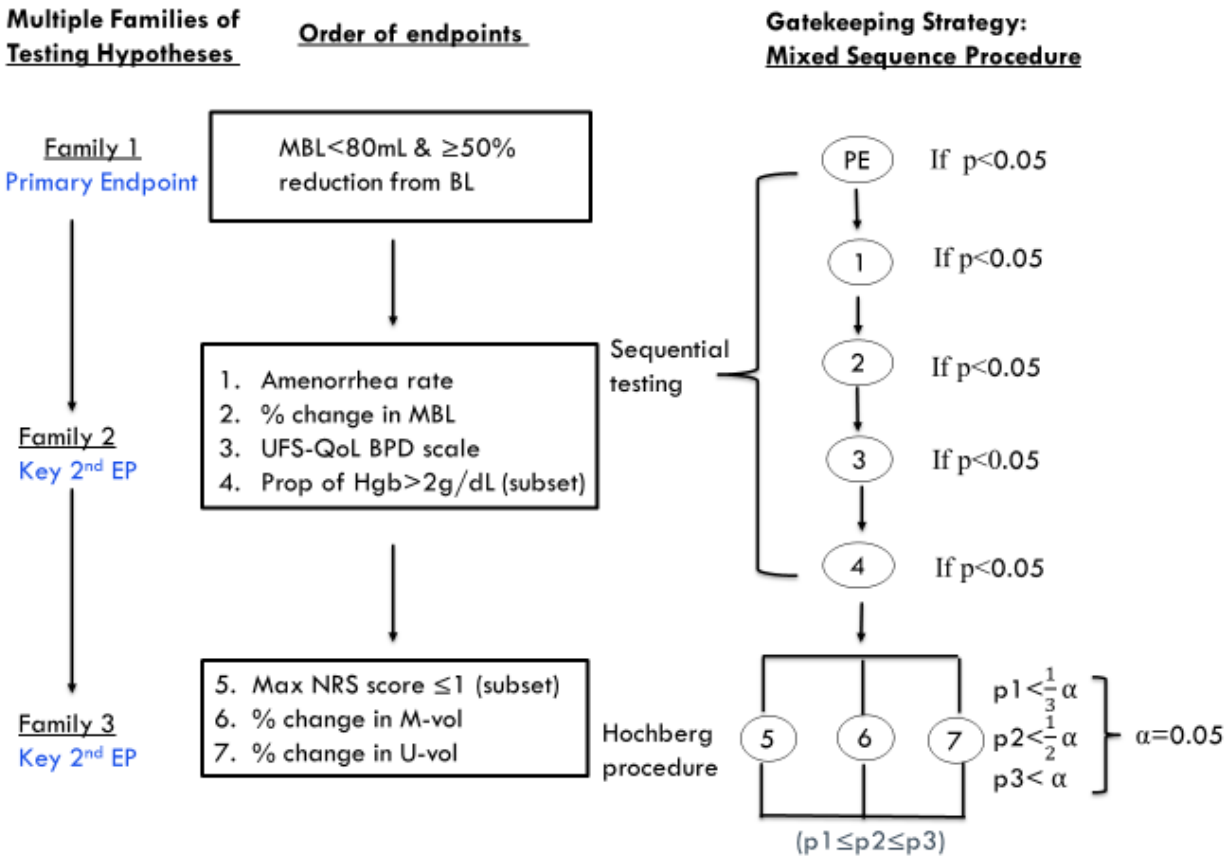
* Defined as those patients who meet the following criteria: eDiary entry rate >70% and no more than 3 consecutive days and no more than 5 days of bleeding/spotting and use of menstrual product reported on the eDiary over the week 24/end of treatment visit window.

Key Secondary Efficacy End Points with Alpha-Protection

For testing whether relugolix combination therapy (Group A) was statistically significantly superior to placebo (Group C) for the primary efficacy end point as well as the seven key secondary end points listed below, a gate-keeping mixed sequence testing procedure was applied to maintain the family-wise type I error rate. Under this testing procedure, the primary end point was tested first at a 2-sided 0.05 significance level. If the P-value for primary end point was <0.05, the seven key end points listed below were tested sequentially in the order depicted in Figure S1 and Figure S2.

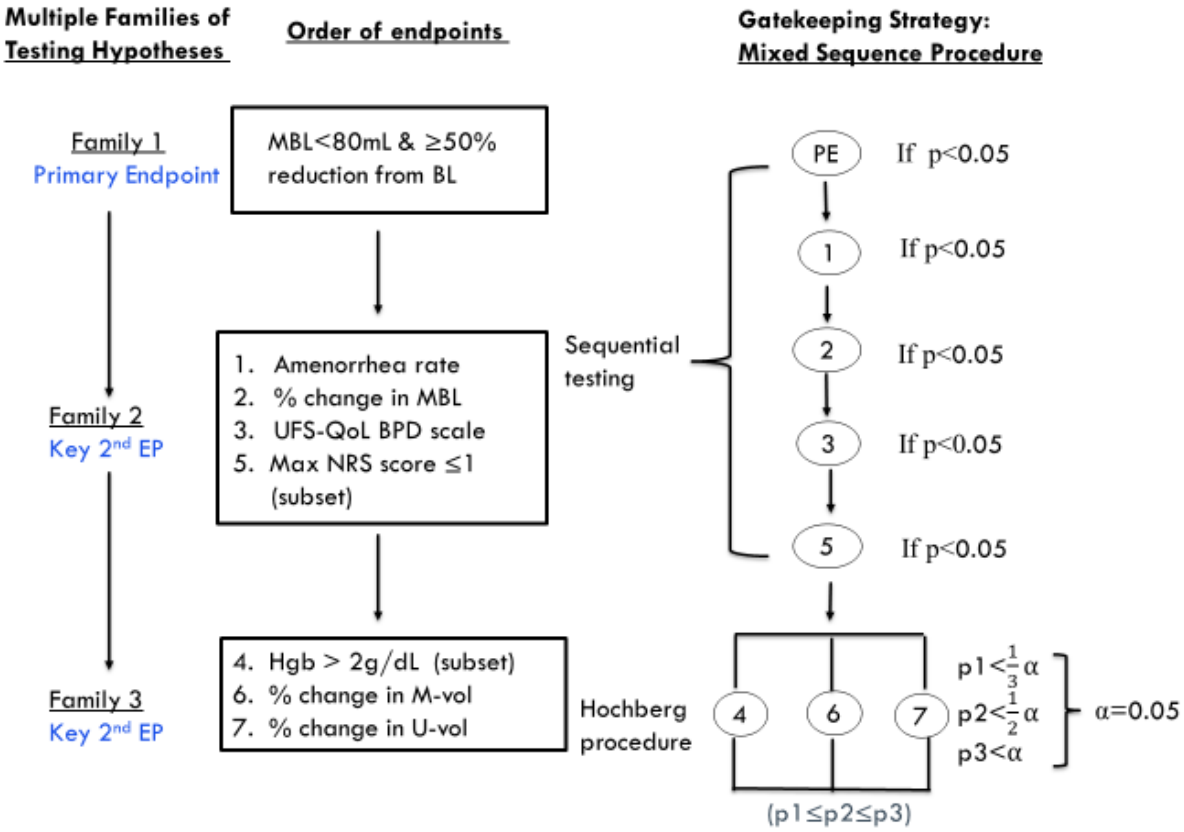
For the relugolix combination therapy group to be considered statistically superior to the placebo group on a secondary end point, the two-sided P-value must be <0.05 for that secondary end point and for all higher-ranking secondary end points, as well as for the primary end point. If the two-sided P-value was <0.05 for the fourth end point (proportion of women with a hemoglobin ≤ 10.5 g per deciliter at baseline who achieve an increase of >2 g per deciliter 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 LIBERTY 2), the remaining three end points (the fifth, sixth, or seventh) were tested using the Hochberg step-up procedure. The fourth end point tested for LIBERTY 2 (Figure S2) was changed (i.e., reordered relative to LIBERTY 1) after results became available from LIBERTY 1 (Figure S1) but before data unblinding of LIBERTY 2.

Figure S1. Mixed Sequence Testing Procedure for Primary and Key Secondary End Points in LIBERTY 1.



BPD denotes Bleeding and Pelvic Discomfort, EP end point, Hgb hemoglobin, max maximum, MBL menstrual blood loss, M-vol myoma volume, NRS Numerical Rating Scale, PE primary end point, Prop proportion, UFS-QoL BPD Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort, and U-vol uterine volume.

Figure S2. Mixed Sequence Testing Procedure for Primary and Key Secondary End Points in LIBERTY 2.



From the Hochberg procedure, the P-values were calculated for the three end points (5, 6, and 7 for LIBERTY 1 and 4, 6, and 7 for LIBERTY 2) and ranked from the smallest to the largest. The end point corresponding to the largest P-value gets tested first. If the P-value was <0.05, then no further testing occurred, and it was concluded that all three end points are positive. Otherwise, the end point corresponding to the second largest P-value was tested. If the P-value was <0.025, then no further testing occurred, and it was concluded that the end points corresponding to the middle and smallest P-values are positive. Otherwise, the end point with the smallest P-value was tested. If the P-value was <0.0167, no further testing occurred, and it was concluded that only the end point with the smallest P-value was positive. Otherwise, all three end points did not pass the statistical significance criterion at 0.05 level.

The seven key secondary efficacy end points are numbered 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 per deciliter at baseline who achieve an increase of >2 g per deciliter 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 end points (1, 4, and 5) that are evaluating proportions, treatment comparisons were 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 were provided.

For key secondary end point 4, an increase in hemoglobin of 2g per deciliter was 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 end point 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/end of treatment maximum value are determined as follows.

Because patients were asked to begin electronic diary entries after returning the first collection of menstrual products, the number of electronic diary 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 was ended and the number of pain score days at baseline could be as short as 7 days or as long as 70 days prior to randomization. If a patient met the subset definition (maximum NRS score ≥4 at baseline) over a portion of the screening days (e.g., 7–70 days), she also met the subset definition on the entire 35 days interval.

Since the maximum NRS value was 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/end of treatment was 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 end point 5 was analyzed for the subset of women who had a maximum pain score ≥4 during the 35 days prior to randomization and who had at least 28 days (80% of the last 35 days of treatment) of pain scores recorded in the e-Diary at week 24/end of treatment. In addition, a sensitivity analysis was conducted on the subset of women who had 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 end point 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) was also performed using NRS scores reported on electronic diary during menstrual and non-menstrual days.

For key secondary efficacy end points (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 was used to assess treatment effect with treatment, randomization stratification factors and baseline value as covariates.

For key secondary efficacy end points (2 and 3) evaluating the change (absolute or % change) from baseline to week 24 by ultrasound, treatment comparisons were 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 was assumed for each patient.

Patient-Reported Outcomes

Overview

The justification for evaluating patient-reported outcomes in women with uterine fibroids is the clinical importance of symptomatology. Specifically, the condition may manifest as pain, symptoms related to bleeding and to fibroid bulk, and/or attendant functional, social, and emotional effects that adversely affect quality of life.

In the phase 2 study Japanese study in uterine fibroids, a dose-dependent trend in improvement of pain associated with uterine fibroids was recognized that warranted further investigation in phase 3. As a consequence, an important goal of the pivotal relugolix combination therapy and relugolix monotherapy studies was to more fully characterize the impact of relugolix on pain and other patient-reported outcomes in women with uterine fibroids.

In the relugolix combination therapy LIBERTY studies, a key secondary objective was to describe the effect of relugolix in combination with estradiol and norethindrone acetate compared with placebo on pain associated with uterine fibroids. Pain associated with uterine fibroids was measured daily (i.e., during menstrual as well as non-menstrual days) using the well-recognized and validated numerical rating scale (NRS) by electronic diary. Another key secondary end point was distress due to heavy menstrual bleeding, passing blood clots, and pelvic tightness symptoms (as measured by a validated instrument, the Bleeding and Pelvic Discomfort [BPD] scale [Questions 1, 2, and 5 from Uterine Fibroid Symptoms-Quality of Life [UFS-QoL]).

In the phase 3 Japanese relugolix monotherapy program, a separate study of relugolix in women with moderate to severe pain associated with uterine fibroids was conducted in which pain was the primary end point using the NRS instrument (Osuga, 2019).

Specific Assessments and Instruments

1. Pain: Numerical Rating Scale (NRS)

Selection of Instrument and Method of Assessment

Pain is the second most frequent and debilitating symptom for women with uterine fibroids (David et al. 2016; Foth et al. 2017, Monleon et al. 2018) and therefore was identified as an important end point to measure in the relugolix development program.

Women's pain experience is individual and covers a range of pain symptoms, with dysmenorrhea and pelvic pain frequently mentioned (Donnez et al. 2016). Since pain experience is patient specific, and patients spontaneously report different types of pain (Deal et al. 2011), a general measure of pain associated with uterine fibroids was deemed to be best suited and most appropriate for assessment in the relugolix clinical program.

The pain NRS is a validated, single-item, self-reported measure, which asks respondents to rank their pain on an 11-point scale (Ameade and Mohammed 2016). In chronic pain populations, patients have been found to prefer the NRS over other measures of pain intensity due to the NRS's comprehensibility and ease of completion (Hawker et al. 2011). The NRS measures have been described as less abstract and easier to understand than the visual analogue scale (VAS) (Dworkin et al. 2005). In a summary of studies using different pain scales, the NRS was found to have high compliance rates (Hjermstad et al. 2011). The NRS has been found to be highly correlated to the VAS in patients with rheumatic and other

chronic pain conditions (pain >6 months): correlations range from 0.79 to 0.95, suggesting that both the NRS and VAS are measuring the same concept (Kahl and Cleland 2005; Hawker et al. 2011).

In the relugolix clinical program, women were asked to document in a patient electronic diary the worst pain associated with their uterine fibroids that they had experienced during the last 24 hours on a scale from 0 to 10, with 0 indicating "no pain" and 10 indicating "pain as bad as you can imagine." Recording of "worst pain" helps mitigate the confounding issue of timing of the reporting of the NRS versus timing of analgesic administration, the latter of which would be expected to lower the pain score.

End Points

In the pivotal relugolix combination therapy LIBERTY studies, the proportion of women who achieved a maximum NRS score for pain associated with uterine fibroids over the last 35 days of treatment that was ≤ 1 (minimal to no pain) was a key secondary end point in the subset of women with a maximum pain score of ≥4 (moderate to severe pain) during the time period prior to randomization and who completed the daily electronic diary during the 35 days prior to randomization (pain-evaluable population).

Similarly, in the relugolix Japanese study, which enrolled only women with a maximum pain score of ≥4 (moderate to severe pain) at baseline, the proportion of women who achieved a maximum NRS score for pain associated with uterine fibroids of ≤ 1 (minimal to no pain) over the last 28 days of treatment was reported as the primary end point.

NRS Thresholds for Analyses

The threshold of a maximum pain score of ≤ 1 was chosen for the phase 3 studies because patient reports of minimal to no pain would represent the maximal improvement possible. Analgesic use was analyzed for the pain-evaluable population as supportive data to the primary analysis of the proportion of patients meeting the NRS threshold.

The pivotal studies with relugolix combination therapy also assessed as a supportive secondary end point, the percentage of patients with a 30% reduction from baseline in NRS score. Traditionally, pain reductions from baseline of at least 30% have been used as a threshold of clinically meaningful change in chronic pain clinical studies (Dworkin et al. 2005).

2. Bleeding and Pelvic Discomfort: BPD Scale

A key secondary end point in the pivotal relugolix combination therapy studies was the change from baseline to week 24 in the UFS-QoL BPD scale score, with a range of possible scores from 0 to 100, where higher scores are indicative of greater distress and lower scores are indicative of less distress.

The UFS-QoL BPD scale was derived and validated by Myovant using exploratory and confirmatory factor analysis. It assesses distress experienced by patients due to three symptoms associated with uterine fibroids that are common to most patients (i.e., 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]) (Spies et al. 2002). Questions 1 and 2 are closely related to the primary end point, they provide the patient perspective in terms of distress due to heavy bleeding and passing blood clots, while the primary end point objectively measures blood loss volume. Question 5 is the expected patient symptomatology that is related to the uterine volume end point.

The meaningful change threshold for the BPD was derived via anchor-based analyses using pooled blinded data from the first third of patients enrolled in one of the two LIBERTY studies, who completed

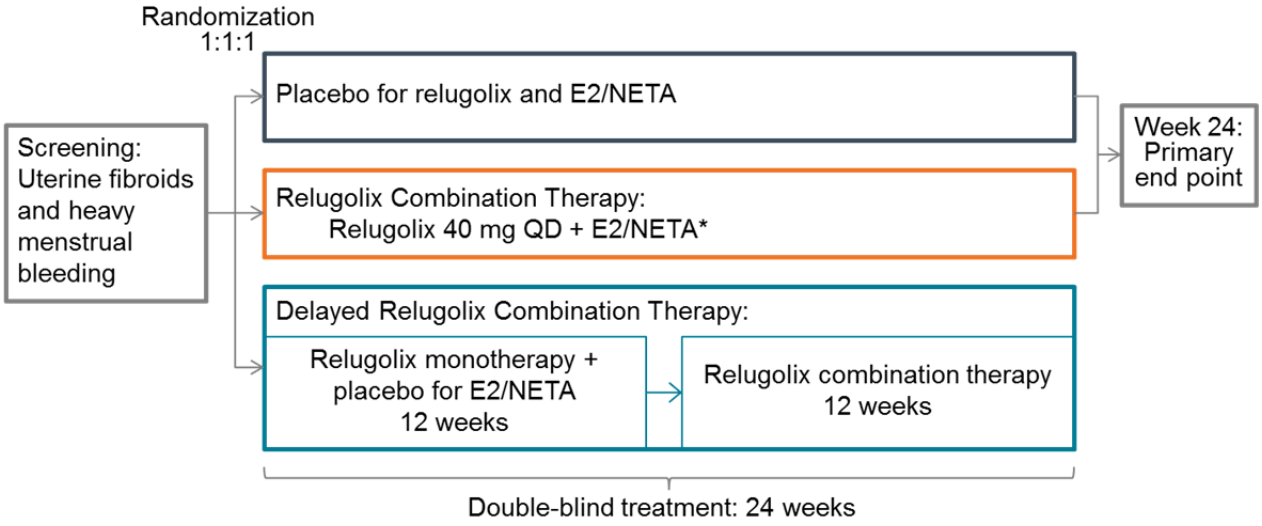
week 24 visits and had PGA scores for symptoms at baseline and week 24. Findings were supported by the results from the qualitative exit interview study, in which the patients' perception of what constitutes a meaningful change on the BPD scale was assessed. The meaningful change threshold was set at 20 points, based on the totality of data from anchor-based analyses from blinded phase 3 data, supported by cumulative distribution function and probability density function curves as well as the results from the exit interview study. As illustrated in the cumulative distribution function curves (Supplementary Methods), setting the meaningful change threshold at 20-point improvement on the BPD scale would yield a percent of misclassified responders for the "no change" group of 33% and a percent of correctly classified responders of 60% for the "1 category improvement" group.

The BPD scale was only assessed as an end point in the relugolix combination therapy LIBERTY studies and not in the relugolix monotherapy program.

Description of development and validation of the BPD instrument has been presented (Li et al. 2019) and is under preparation as a separate manuscript.

Supplementary Figures

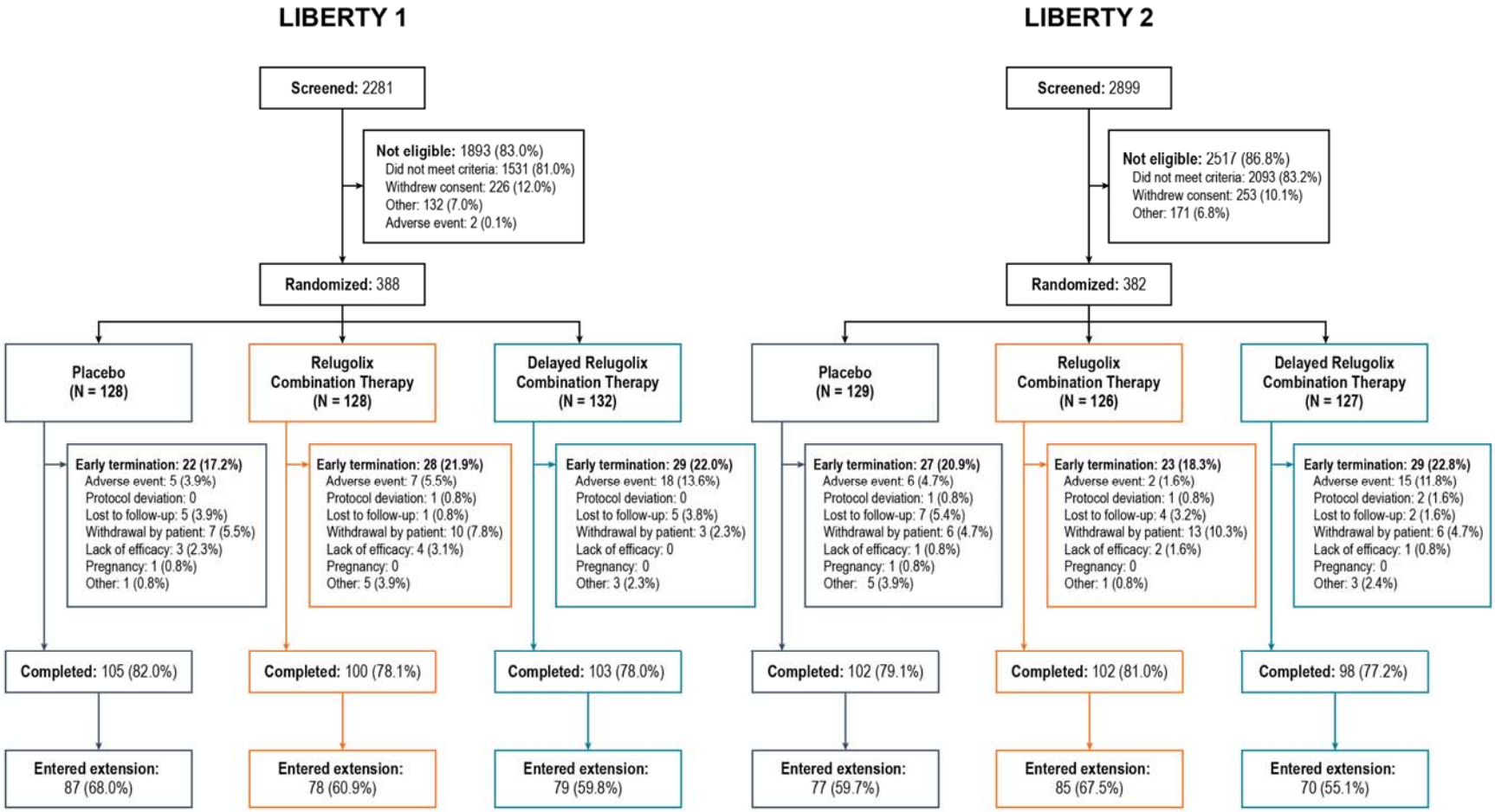
Figure S3. Study Design.



E2 denotes estradiol, NETA norethindrone acetate, and QD once a day.

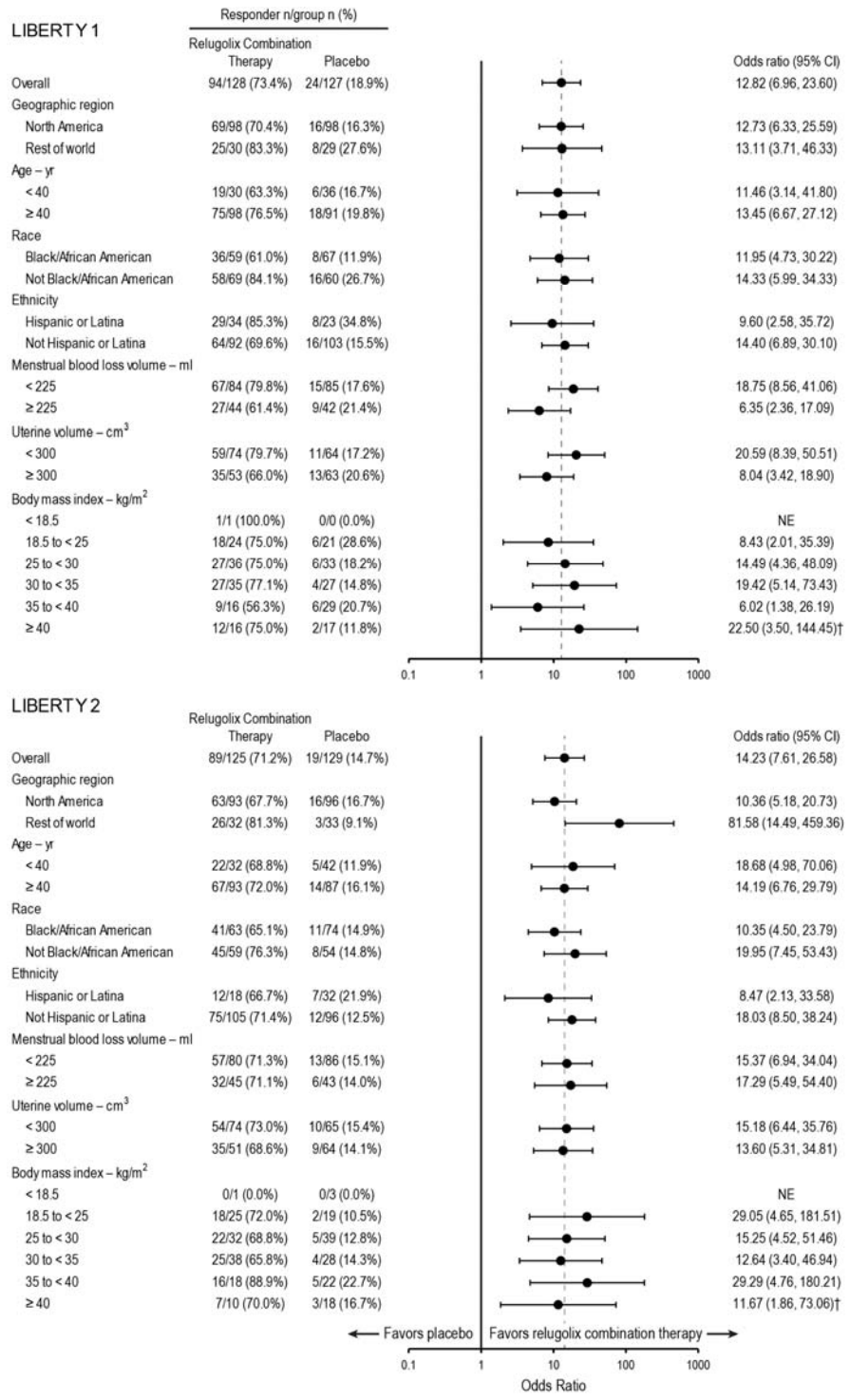
* E2 1 mg, NETA 0.5 mg.

Figure S4. Patient Disposition.



Patients not meeting eligibility criteria due to lack of confirmation of uterine fibroids or heavy menstrual bleeding: LIBERTY 1, 971 (63.4%); LIBERTY 2, 1202 (57.4%).

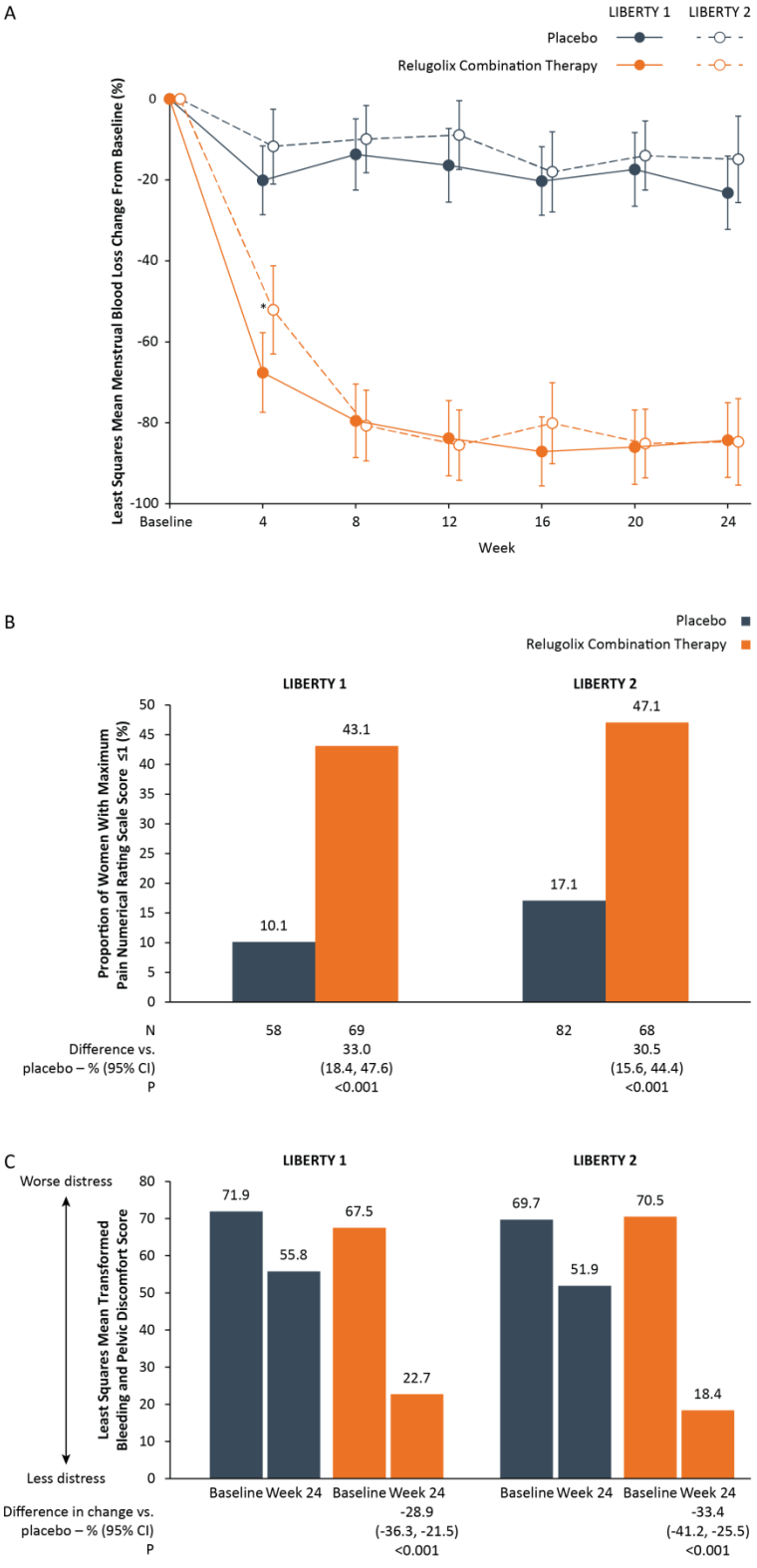
Figure S5. Subgroup Analyses for Primary End Point.*



* Primary end point is the proportion of responders with menstrual blood loss volume < 80 mL and ≥ 50% reduction from baseline over the last 35 days of treatment. All variables are at baseline. Unless otherwise noted, odds ratios are based on logistic regression with treatment group, baseline menstrual blood loss volume, and geographic region (North America, Rest of World) as covariates. CI denotes confidence interval and NE not estimable. 95% CIs are not adjusted for multiplicity and thus should not be used to infer definitive treatment effects.

† Odds ratio based on logistic regression with treatment group as the only covariate due to smaller sample size.

Figure S6. Secondary Efficacy End Points: A) Reduction in Menstrual Blood Loss, B) Relief of Pain Associated With Uterine Fibroids, and C) Reduction in Bleeding and Pelvic Discomfort.



In A, least squares means and P value for test of difference of relugolix combination therapy minus placebo was based on a mixed-effects model with baseline menstrual blood loss, region, treatment, visit, and treatment by visit as fixed effects; lines are staggered for visibility. In B, results are analyzed for the patient subgroup with moderate/severe pain (Numerical Rating Scale score ≥4) associated with uterine fibroids during the 35 days prior to randomization and at least 28 days of electronic daily diary entries during the last 35 days of treatment. In C, the Bleeding and Pelvic Discomfort transformed score ranges from 0 to 100, with higher scores indicating greater symptom severity. CI denotes confidence interval.
*Data shown for LIBERTY 2 are from a sensitivity analysis excluding a week-4 menstrual blood loss volume of 2710 mL for one woman in the relugolix combination therapy arm (menstrual blood loss data from this patient were included at all other time points). The week-4 least squares mean menstrual blood loss change from baseline in the pre-specified analysis with this outlying week-4 data point included was 36.1% (95% CI 57.2%, 15.0%; nominal P=0.055 vs. placebo) and in the sensitivity analysis with this data point excluded was 52.1% (95% CI: 63.0%, 41.2%, nominal P<0.001 vs. placebo).

Supplementary Tables

Table S4. Additional Baseline Characteristics.

	LIBERTY 1			LIBERTY 2		
	Placebo (N = 127)	Relugolix Combination Therapy (N = 128)	Delayed Relugolix Combination Therapy (N = 132)	Placebo (N = 129)	Relugolix Combination Therapy (N = 125)	Delayed Relugolix Combination Therapy (N = 127)
Geographic Region – no. (%)						
North America	98 (77.2)	98 (76.6)	101 (76.5)	96 (74.4)	93 (74.4)	94 (74.0)
Rest of world	29 (22.8)	30 (23.4)	31 (23.5)	33 (25.6)	32 (25.6)	33 (26.0)
Hypertension – no. (%)	23 (18.1)	33 (25.8)	21 (15.9)	24 (18.6)	23 (18.3)	29 (23.0)

Table S5. Other Secondary End Points.

End Point Statistics	LIBERTY 1 Placebo (N = 127)	LIBERTY 1 Relugolix Combination Therapy (N = 128)	LIBERTY 1 Delayed Relugolix Combination Therapy (N = 132)	LIBERTY 2 Placebo (N = 129)	LIBERTY 2 Relugolix Combination Therapy (N = 125)	LIBERTY 2 Delayed Relugolix Combination Therapy (N = 127)
Percent change from baseline to week 24 in hemoglobin concentrations for women with hemoglobin ≤10.5 g per deciliter at baseline						
LS mean ±SE	10.0±3.5	20.8±3.1	24.6±3.0	4.3±2.7	24.3±3.0	29.4±3.0
95% CI	3.0, 17.0	14.7, 26.8	18.6, 30.5	-1.1, 9.6	18.3, 30.3	23.5, 35.3
Difference of LS mean ±SE*		10.8±4.2	14.6±4.2		20.0±3.9	25.1±3.9
95% CI		2.5, 19.2	6.4, 22.9		12.3, 27.8	17.4, 32.9
Patients with a hemoglobin concentration below the lower limit of normal† who achieved an increase of ≥1 g per deciliter from baseline to week 24						
Patients with hemoglobin below lower limit of normal at baseline – no. (%)	67 (52.8)	72 (56.3)	83 (62.9)	81 (62.79)	69 (55.2)	75 (59.1)
no. (%)	17 (25.4)	34 (47.2)	46 (55.4)	18 (22.2)	35 (50.7)	44 (58.7)
95% CI – %‡	15.53, 37.49	35.33, 59.35	44.10, 66.34	13.73, 32.83	38.41, 62.98	46.70, 69.92
Difference from placebo (95% CI) – %§		21.85 (6.31, 37.39)	30.05 (15.12, 44.98)		28.50 (13.63, 43.37)	36.44 (22.09, 50.80)
Responders with a meaningful reduction of ≥20 points from baseline to week 24 in BPD scale score						
no. (%)	35 (27.6)	79 (61.7)	83 (62.9)	37 (28.7)	79 (63.2)	69 (54.3)
95% CI – %‡	20.01, 36.19	52.72, 70.17	54.04, 71.12	21.07, 37.30	54.11, 71.65	45.26, 63.19
Difference from placebo (95% CI) – %§		34.16 (22.70, 45.62)	35.32 (23.99, 46.65)		34.52 (23.01, 46.02)	25.65 (13.99, 37.31)

BPD denotes Bleeding and Pelvic Discomfort, CI confidence interval, LS least squares, and SE standard error.

* Based on mixed-effects model with treatment, visit, region, baseline menstrual blood loss and treatment-by-visit interaction included as fixed effects. The multiple visits for each patient were the repeated measures as a random effect within each patient and an unstructured covariance.

† Lower limit of normal is hemoglobin <11.6 g per deciliter.

‡ Based on exact binomial 95% CI (Clopper-Pearson).

§ Difference is Relugolix combination therapy or Delayed relugolix combination therapy minus Placebo. 95% CI for difference is based on the normal approximation not adjusted for multiplicity, and thus should not be used to infer definitive treatment effects.

Table S6. Serious Adverse Events.*

Serious adverse events – no. (%)	LIBERTY 1			LIBERTY 2		
	Placebo (N = 127)	Relugolix Combination Therapy (N = 128)	Delayed Relugolix Combination Therapy (N = 132)	Placebo (N = 129)	Relugolix Combination Therapy (N = 126)	Delayed Relugolix Combination Therapy (N = 126)
At least one	2 (1.6)	7 (5.5)	3 (2.3)	4 (3.1)	1 (0.8)	2 (1.6)
Ankle fracture	0	1 (0.8)	1 (0.8)	0	0	0
Avulsion fracture	0	1 (0.8)	0	0	0	0
Hematemesis	0	1 (0.8)	0	0	0	0
Hypothyroidism	0	1 (0.8)	0	0	0	0
Menorrhagia	0	1 (0.8)	0	0	0	0
Pelvic pain	0	1 (0.8)	0	0	0	0
Rhabdomyolysis	0	1 (0.8)	0	0	0	0
Uterine leiomyoma	0	1 (0.8)	0	0	0	0
Uterine myoma expulsion	0	1 (0.8)	0	**0**	0	0
Vitreous detachment	0	1 (0.8)	0	0	0	0
Acute psychosis	1 (0.8)	0	0	0	0	0
Appendicitis	0	0	1 (0.8)	0	0	0
Panic attack	0	0	1 (0.8)	0	0	0
Pneumonia	1 (0.8)	0	0	0	0	0
Cholecystitis	0	0	0	0	1 (0.8)	0
Anemia	0	0	0	1 (0.8)	0	0
Cholecystitis acute	0	0	0	0	0	1 (0.8)
Intervertebral disc degeneration	0	0	0	0	0	1 (0.8)
Intervertebral disc protrusion	0	0	0	0	0	1 (0.8)
Necrotising fasciitis	0	0	0	1 (0.8)	0	0
Radius fracture	0	0	0	1 (0.8)	0	0
Road traffic accident	0	0	0	1 (0.8)	0	0
Syncope	0	0	0	1 (0.8)	0	0

* Adverse events were coded using the *Medical Dictionary for Regulatory Activities* and severity of adverse events was evaluated by the investigator based on the National Cancer Institute's *Common Terminology for Adverse Events* (version 5.0).

Table S7. Percent Change from Baseline in Bone Mineral Density at Lumbar Spine and Total Hip in LIBERTY 1 and LIBERTY 2.

	LIBERTY 1			LIBERTY 2		
Location **Time point** **Statistic**	**Placebo (N = 127)**	**Relugolix combination therapy (N = 128)**	**Delayed relugolix combination therapy (N = 132)**	**Placebo (N = 129)**	**Relugolix combination therapy (N = 126)**	**Delayed relugolix combination therapy (N = 126)**
Lumbar spine						
Week 12						
no.	103	101	103	104	103	95
LS mean percent change from baseline (95% CI)	0.20 (-0.36, 0.76)	-0.47 (-1.04, 0.10)	-2.00 (-2.56, -1.43)	0.51 (-0.01, 1.03)	-0.82 (-1.35, -0.29)	-1.92 (-2.46, -1.37)
Week 24						
no.	102	100	100	95	95	94
LS mean percent change from baseline (95% CI)	0.05 (-0.52, 0.62)	-0.36 (-0.93, 0.22)	-1.82 (-2.39, -1.25)	0.32 (-0.26, 0.89)	-0.13 (-0.71, 0.46)	-2.12 (-2.71, -1.53)
Total hip						
Week 12						
no.	104	102	100	102	104	93
LS mean percent change from baseline (95% CI)	0.41 (-0.03, 0.85)	0.01 (-0.45, 0.46)	-0.95 (-1.40, -0.50)	-0.16 (-0.56, 0.24)	0.05 (-0.35, 0.45)	-1.07 (-1.48, -0.65)
Week 24						
no.	103	100	98	95	98	92
LS mean percent change from baseline (95% CI)	0.55 (0.08, 1.02)	0.02 (-0.46, 0.51)	-1.04 (-1.52, -0.56)	-0.04 (-0.48, 0.39)	-0.17 (-0.61, 0.26)	-1.16 (-1.60, -0.71)

CI denotes confidence interval and LS least squares.

Table S8. Summary of Patients With Liver Function Tests Meeting Predefined Limits of Change.

Patients – no. (%)	LIBERTY 1			LIBERTY 2		
	Placebo (N = 127)	Relugolix Combination Therapy (N = 128)	Delayed Relugolix Combination Therapy (N = 132)	Placebo (N = 129)	Relugolix Combination Therapy (N = 126)	Delayed Relugolix Combination Therapy (N = 126)
ALT or AST ≥3 × ULN and <5 × ULN	1 (0.8)	1 (0.8)	1 (0.8)	0	0	1 (0.8)
ALT or AST ≥5 × ULN and <10 × ULN	0	0	1 (0.8)	0	0	0
ALT or AST ≥10 × ULN and <20 × ULN	0	0	0	0	0	0
ALT or AST ≥20 × ULN	0	0	0	0	0	0
BILI ≥2 × ULN	0	0	0	0	0	0
ALT or AST ≥3 × ULN and BILI ≥2 × ULN	0	0	0	0	0	0

ALT denotes alanine aminotransferase, AST aspartate aminotransferase, BILI total bilirubin, and ULN upper limit of normal.

Table S9. Summary of Change from Baseline in Serum Lipids.

Parameter Statistics	LIBERTY 1 Placebo (N = 127)	LIBERTY 1 Relugolix Combination Therapy (N = 128)	LIBERTY 1 Delayed Relugolix Combination Therapy (N = 132)	LIBERTY 2 Placebo (N = 129)	LIBERTY 2 Relugolix Combination Therapy (N = 126)	LIBERTY 2 Delayed Relugolix Combination Therapy (N = 126)
Cholesterol – mg/deciliter						
Change from baseline at week 24						
no.	97	92	98	92	91	89
Mean ±SD	-1.9±25.3	-2.1±22.1	2.0±25.1	-0.8±20.8	0.8±31.6	5.5±25.5
Maximum increase from baseline during treatment						
no.	52	46	61	44	51	63
Mean ±SD	14.8±14.1	16.4±12.5	18.1±14.8	17.7±11.9	22.7±22.5	18.2±16.9
LDL cholesterol – mg/deciliter						
Change from baseline at week 24						
no.	97	92	96	92	90	89
Mean ±SD	-2.8±21.2	0.3±18.2	0.9±20.8	-0.7±17.4	2.6±28.3	4.6±21.9
Maximum increase from baseline during treatment						
no.	54	53	53	49	57	57
Mean ±SD	11.8±11.9	12.2±11.1	15.8±11.4	13.0±11.1	17.9±21.6	17.3±15.2
HDL cholesterol – mg/deciliter						
Change from baseline at week 24						
no.	97	92	98	92	91	89
Mean ±SD	0.1±9.7	-1.2±8.4	0.2±7.9	1.8±7.3	-1.0±7.9	0.3±7.0
Maximum decrease from baseline during treatment						
no.	50	58	54	47	60	44
Mean ±SD	-7.2±7.5	-6.3±5.2	-5.5±5.3	-4.6±3.8	-6.4±5.4	-4.5±3.6

Parameter Statistics	LIBERTY 1 Placebo (N = 127)	LIBERTY 1 Relugolix Combination Therapy (N = 128)	LIBERTY 1 Delayed Relugolix Combination Therapy (N = 132)	LIBERTY 2 Placebo (N = 129)	LIBERTY 2 Relugolix Combination Therapy (N = 126)	LIBERTY 2 Delayed Relugolix Combination Therapy (N = 126)
Triglycerides – mg/deciliter						
Change from baseline at week 24						
no.	97	92	98	92	91	89
Mean ±SD	5.2±44.8	-4.0±45.9	4.8±49.3	-9.1±50.0	-4.7±58.0	3.0±44.7
Maximum decrease from baseline during treatment						
no.	58	45	63	43	44	55
Mean ±SD	29.3±38.9	31.0±29.2	31.6±32.8	28.6±26.4	40.0±40.0	33.1±33.5

HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and SD standard deviation.

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