Protocol

Protocol for: Gounder M, Ratan R, Alcindor T, et al. Nirogacestat, a γ-secretase inhibitor for desmoid tumors. N Engl J Med 2023;388:898-912. DOI: 10.1056/NEJMoa2210140

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

SUPPLEMENTARY APPENDIX: PROTOCOL AND STATISTICAL ANALYSIS PLANS

This supplement contains the following items:

1. Original protocol, final protocol, and summary of amendments

2. Original main analysis plan, final main statistical analysis plan, and summary of amendments

3. Original patient-reported outcomes statistical analysis plan, final patient-reported outcomes statistical analysis plan, and summary of amendments

Title Page

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Protocol Number: NIR-DT-301

Compound Number: PF-03084014 (nirogacestat)

Study Phase: Phase 3

Short Title: A Placebo-Controlled, Phase 3 Study of Nirogacestat in Adults with Desmoid Tumor/Aggressive Fibromatosis (DT/AF).

Sponsor Name: SpringWorks Therapeutics

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Regulatory Agency Identifier Number(s)

Registry	ID
EudraCT	2018-001991-39
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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Short Title: A Placebo-Controlled, Phase 3 Study of Nirogacestat in Adults with Desmoid Tumor/Aggressive Fibromatosis (DT/AF).

Rationale:

The NIR-DT-301 Phase 3, double-blind, placebo-controlled study is being conducted to determine the efficacy and safety of nirogacestat in participants with progressing desmoid tumors. A Phase 1 solid tumor study provided preliminary efficacy (Messersmith, 2015), including long-term durable responses and safety of nirogacestat in desmoid participants (Villalobos, 2018). These encouraging results lead to a Phase 2 study in participants with progressing desmoid tumors (Kummar, 2017). This study demonstrated that nirogacestat resulted in a 29% response rate, significant tumor shrinkage as measured by magnetic resonance imaging (MRI) and no participants progressing while on therapy. Importantly, participants in the responder group had failed previous systemic therapies (imatinib or sorafenib) indicating a need for alterative therapeutic options for this patient population. These results support the further study of nirogacestat in this population.

Objectives and Endpoints

Key Objectives	**Key Endpoints**
Primary	**Primary**
To determine the efficacy (as defined by progression free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF.	PFS defined as the time from randomization until the date of assessment of progression or death by any cause will be determined using Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1 (Eisenhauer, 2009; Section 10.9). The documented date of progression will be determined by an independent, blinded, central radiologic review.

Key Objectives	**Key Endpoints**
Secondary	**Secondary**
To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of adverse events (AEs);	Safety endpoints will include incidence of treatment-emergent AEs, changes in laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs). Tolerability will be assessed according to toxicities graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0;
To determine the overall response rate (complete response [CR] + partial response [PR]) of nirogacestat in participants with progressing DT/AF;	Overall response rate, defined as the proportion of participants with CR + PR assessed by RECIST v1.1 criteria;
To determine the duration of response;	Duration of response for participants whose best response is CR or PR;
To compare tumor volume changes measured by MRI in participants with progressing DT/AF; and	Change in tumor volume from baseline as assessed by MRI volumetric; and
To evaluate desmoid tumor symptoms and impacts using patient-reported outcomes (PROs).	Symptoms and impacts will be assessed by evaluating change from baseline on the desmoid-specific PRO assessment, MD Anderson symptom inventory (MDASI), and brief pain inventory (BPI) short form.

Overall Design:

This is a multi-center, randomized, double-blind, placebo-controlled, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. This study will consist of 2 phases, a double-blind and an optional open-label extension (OLE) phase.

Participants will be screened up to 28 days prior to the first dose of study treatment in the double-blind phase and eligibility will be based on the inclusion and exclusion criteria (Sections 5.1 and 5.2). Refer to the double-blind schedule of activities (SoA) (Section 1.3.1) for the required assessments and Table 6 for additional details regarding each scheduled study visit.

Following disease progression (confirmed by central review using RECIST v1.1), or completion of the double-blind phase (once the required number of events have been observed and the primary PFS analysis has been completed), participants' treatment assignment will be unblinded, and if eligible, participants will have the option to enroll in the optional OLE phase (Section 6.7.1). Refer to OLE SoA (Section 1.3.2) for the required assessments and Table 7 for additional details regarding each scheduled study visit.

See Section 1.2 for study schema.

Disclosure Statement: This is a randomized, parallel treatment study with 2 arms that is participant and investigator blinded. There is an optional OLE phase for eligible participants.

Number of Participants:
Approximately 105 participants will be screened (assessed for eligibility) to achieve 94 participants randomly assigned (1:1) to study treatment (placebo or nirogacestat). It is estimated that 51 observed progression events will be needed to meet the primary PFS analysis. Refer to Section 9.2 for sample size determination.

Treatment Groups and Duration:

Double-blind phase:

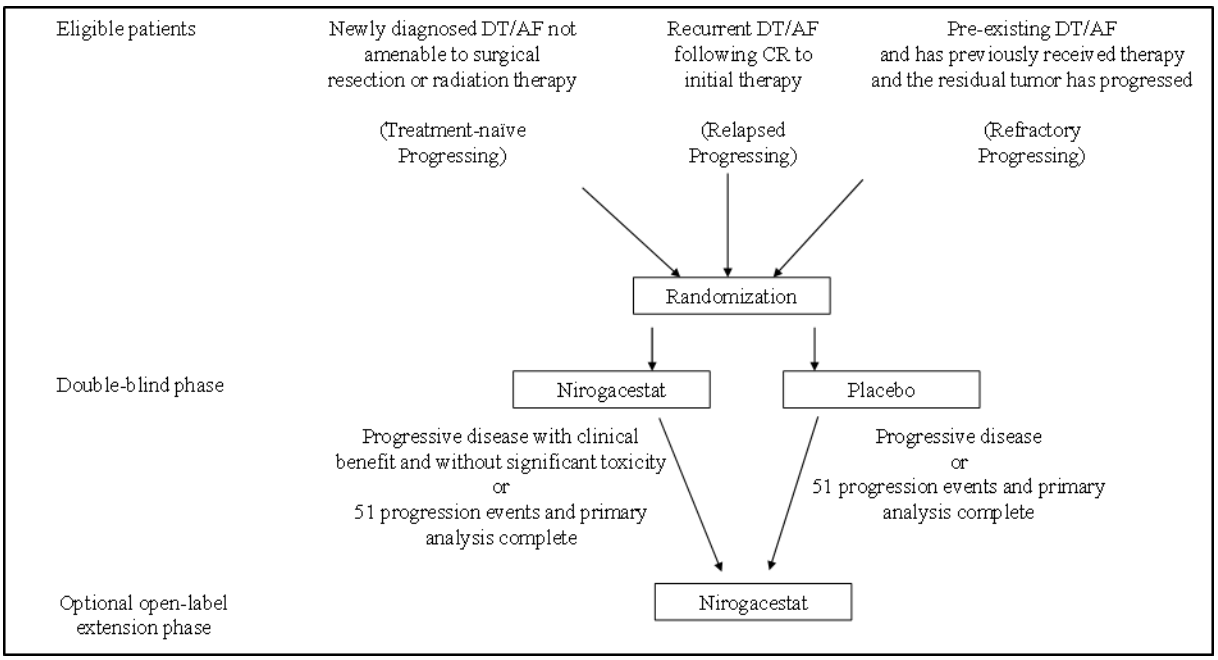
At Cycle 1 Day 1 (baseline), participants will be randomized (stratified by primary tumor location) to study treatment (nirogacestat or placebo) in a 1:1 ratio and will receive 150 mg BID of study treatment, continually in 28-day cycles. Participants will remain in the double-blind phase until death, disease progression (confirmed by central review using RECIST v1.1), they prematurely discontinue study treatment for any reason, the study is stopped by the sponsor for any reason, or the required number of PFS events have been observed and the primary PFS analysis has been completed (based on current statistical assumptions, this is anticipated to be approximately 2 years after the first participant is randomized).

Open-label phase:

Eligible participants (refer to Sections 6.7.2 and 6.7.3 for OLE eligibility criteria) may enroll in the optional OLE phase to receive 150 mg BID of nirogacestat (open-label study treatment), continuously in 28-day cycles. Participants will remain in the OLE phase until death, disease progression (confirmed by central review using RECIST v1.1), they prematurely discontinue study treatment for any reason, the study is stopped by the sponsor for any reason, or nirogacestat is commercially available.

Data Monitoring Committee: Yes

1.2. **Schema**



DT/AF = desmoid tumor/aggressive fibromatosis; CR = complete response.

1.3. Schedule of Activities (SoA)

1.3.1. Double-Blind Phase SoA

Cycle Number Cycle Day	**Screening[1]**	**Cycle 1 Day 1 Baseline[3]**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 1 Day 22**	**Cycle 2 Day 1**	**Cycle 4 Day 1**	**Cycle 7 Day 1 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Visit Week (Calendar Day)		**Week 1 (Day 1)**	**Week 2 (Day 8)**	**Week 3 (Day 15)**	**Week 4 (Day 22)**	**Week 5 (Day 29)**	**Week 13 (Day 85)**	**Week 25 (Day 169) & On**		
Visit Window	**Up to 28 days before Day 1**	**Up to 48 hours prior to first dose**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**See footnote 27**	**30 days (+7 days) after last dose**
Informed consent[2]	X									
I/E criteria	X	X								
Demography	X									
Medical history	X									
ECOG performance status[4]	X	X				X	X	X	X	X
Physical examination[5]	X[5a]	X[5a]	X[5b]	X[5b]	X[5b]	X[5b]	X[5a]	X[5a]	X[5a]	X[5a]
Vital signs[6]	X	X	X	X	X	X	X	X	X	X
Weight/height[7]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[8]	X	X[8a]	X[8b]			X	X	X	X	X
Laboratory										
Tumor biopsy[9]	X[9a]								X[9b] (optional)	
Blood for serology[10]	X									
Blood for serum pregnancy test (WOCBP only)[11]	X									
Blood for PK sampling[12]		X[12a]	X[12b]							
Blood for pharmacogenomics (optional)[13]		X (optional)								
Blood for genotyping[14]		X								
Blood for clinical chemistry[15]	X	X	X	X	X	X	X	X	X	X
Urinalysis[16]	X	X				X	X	X	X	X
Monthly urine pregnancy test (WOCBP only)[17]		X				←==========		==========→	X	X

Cycle Number Cycle Day	**Screening[1]**	**Cycle 1 Day 1 Baseline[3]**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 1 Day 22**	**Cycle 2 Day 1**	**Cycle 4 Day 1**	**Cycle 7 Day 1 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Visit Week (Calendar Day)		**Week 1 (Day 1)**	**Week 2 (Day 8)**	**Week 3 (Day 15)**	**Week 4 (Day 22)**	**Week 5 (Day 29)**	**Week 13 (Day 85)**	**Week 25 (Day 169) & On**		
Visit Window	**Up to 28 days before Day 1**	**Up to 48 hours prior to first dose**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**See footnote 27**	**30 days (+7 days) after last dose**
Patient-Reported Outcomes[18]										
BPI short form[18a]	X[18c]	X[18c]				←==========→				X
MDASI[18a]	X[18c]	X[18c]				←==========→				X
Desmoid-specific symptoms PRO assessment[18a]	X[18c]	X[18c]				←==========→				X
Desmoid-specific impacts PRO assessment[18b]	X[18c]	X[18c]				←==========→				X
PGIS[18b]	X[18c]	X[18c]				←==========→				X
PGIC[18b]						←==========→				X
Imaging										
Tumor imaging (CT or MRI) using RECIST v1.1[19]	X[19a]						X	X	X[19b]	
Tumor volume assessment (MRI)[20]		X[20a]						X[20b] (every 6 cycles)	X[20c]	
Enrollment and Study Treatment										
Randomization[21]		X								
Study treatment dispensing[22]		X					X	X		
Study treatment administration/diary[23]		←==========→								
Study treatment accountability			X	X	X	X	X	X	X	
Ongoing Monitoring										
Monthly wellness checks[24]	←==========→									
ConMed review	←==========→									
AE/SAE review[25]	←==========→									

AE = adverse event; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; I/E = inclusion/exclusion; MDASI = MD Anderson symptom inventory; MRI = magnetic resonance imaging; PGIS = patient global impression of severity; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = women of childbearing potential; v = version.

1. **Screening visit:** Assessments may occur up to 28 days prior to first dose of study treatment.
2. **Informed consent process:** Includes participant signing the informed consent form (ICF) and must be conducted prior to any study related procedures being performed. Refer to Section 10.1.3 for more detail on the ICF process.
3. **Baseline visit:** Assessments may be performed over a 48-hour period. First dose of study treatment may not occur until ≥day 21 of the screening window to allow for at least one week between the screening and baseline PRO assessments as described in footnote 18c. All baseline assessments are to be conducted prior to first dose of study treatment except for the following assessments: post-dose 12-Lead ECGs and post-dose blood draws for pharmacokinetic (PK) sampling.
4. **Eastern Cooperative Oncology Group (ECOG) performance status:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Section 10.8 for ECOG scale.
5. **Physical examination:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Section 8.2.2 for more detail.

    5a. Complete physical examination is required.

    5b. Brief physical examination is required.
6. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature following at least 5 minutes of rest. At baseline, assessment must be done prior to first dose of study treatment. Refer to Section 8.2.4 for more detail.
7. **Height:** Required at screening only.
8. **12-lead ECGs:** Will be administered in triplicate (2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. ECGs should be performed after vital signs and prior to blood draws, when applicable. Refer to Section 8.2.3 for more detail.

    8a. At baseline, triplicate ECGs are required prior to the first dose of study treatment and approximately 1-hour post-dose.

    8b. At Cycle 1 Day 8, triplicate ECGs are required 1-hour (±10 minutes) post-dose.
9. **Tumor (core needle) biopsy:** Must be done after MRI if assessments occur at the same visit. Refer to Section 8.1.3 and central laboratory manual for sample processing details.

    9a. At screening, tumor biopsy only required if archival tissue is not available for study procedures. Tumor biopsy will be reviewed centrally to confirm or reconfirm diagnosis, but participant enrollment is not dependent on central review.

    9b. At end of treatment (EOT), tumor biopsy will be optional for consenting participants only.

10. **Serology:** Only required at screening and to include testing for hepatitis B virus (hepatitis B surface antigen), hepatitis C virus (hepatitis C antibody [Hepatitis C virus polymerase chain reaction, if hepatitis C antibody positive]), and human immunodeficiency virus. Refer to Section 10.2 and central laboratory manual for sample processing details.

11. **Serum pregnancy test:** Only required at screening for women of childbearing potential (WOCBP). Refer to Sections 8.3.5 and 10.4, and central laboratory manual for sample processing details.

12. **PK sampling:** Refer to Section 8.5 and central laboratory manual for sample processing details.

    12a. At baseline, PK sampling is required at the following timepoints: pre-dose and 0.25, 0.5, 1, 1.5, and 2 hours post-dose. All efforts will be made to obtain within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing and will not be captured as a deviation if the exact time of the sample collection is noted on the source documents and electronic case report form (eCRF).

    12b. At Cycle 1 Day 8, participants will be instructed to **not** take their morning dose at home on the day of this visit. Instead, the morning dose will be taken at the site immediately following pre-dose PK sample.

13. **Pharmacogenomics:** Optional blood sample for consenting participants only. At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Sections 8.8 and 10.5, and central laboratory manual for sample processing details.

14. **Genotyping:** Required blood sample for all participants unless prohibited by local regulations. At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Section 8.7 and central laboratory manual for sample processing details.

15. **Clinical chemistry (hematology and serum chemistry):** At baseline, must be done prior to first dose of study treatment. Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details.

16. **Urinalysis:** At baseline, must be done prior to first dose of study treatment. Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results.

17. **Monthly urine pregnancy tests:** Only required for WOCBP. In between study visits, participants will administer home urine dipstick pregnancy tests and record the results in a home electronic PRO (ePRO) device (both are provided by the sponsor). At baseline, must be done prior to first dose of study treatment to reconfirm eligibility. Refer to Sections 8.2.6 and 10.4 for more detail.

18. **Patient-reported outcomes (PROs):** Questionnaires should be completed before any other assessments/study procedures and before discussion of disease progression to avoid bias in the participant's responses to the questions. Participants will complete the PRO assessments monthly using the home ePRO device throughout the study and always prior to a study visit when applicable. PROs will always be administered in this order: (1) BPI short form, (2) MDASI, (3) desmoid-specific symptoms PRO assessment, (4) desmoid-specific impacts PRO assessment, (5) patient global impression of severity (PGIS), and (6) patient global impression of change (PGIC). Refer to Section 8.1.2 and study reference manual for more detail.

    18a. BPI short form, MDASI and desmoid-specific symptoms PRO assessment will be administered for 7 consecutive days (with a 24-hour recall period).

    18b. Desmoid-specific impacts PRO assessment, PGIS and PGIC will be administered on the last day of the 7-day PRO assessments noted in footnote 18a (with a 7-day recall period). The PGIC is omitted at screening and baseline.

18c. On day 1 of screening, participants will be trained on the home ePRO device and will complete the screening PROs over the next 7 days. The baseline PROs will be administered 7 days prior to the baseline visit with at least 1 week between the screening and baseline PRO assessments.

19. **Tumor imaging:** CT (contrast required unless contraindicated) or MRI (no contrast required) using RECIST v1.1 (modality to be determined by the investigator) is required. Whichever imaging modality is used to measure the tumor by RECIST v1.1 at screening must be used at each subsequent visit. All scans will be submitted and reviewed centrally, but participant enrollment is not dependent on central review. Refer to Section 8.1.1.1 and imaging manuals for more detail.

    19a. Scans acquired prior to participant signing ICF may be used as screening time point scans if they were obtained within 28 days of the first dose of study treatment and participant meets study requirements. These scans will then be collected, stored, and documented as the screening scan. No other pre-enrollment images will be collected or stored for the study.

    19b. At EOT, scan is only required if not performed within the past 3 months.

20. **Tumor volume assessment:** Tumor volume will be assessed using MRI (no contrast required). If applicable during the study treatment period, CT and MRI assessments may be conducted on the same day. However, MRI with no contrast must be performed prior to CT with contrast. MRI must be done prior to tumor biopsy if assessments occur on the same visit. Refer to Section 8.1.1.2 and imaging manuals for more detail.

    20a. At baseline, MRI is not required if used to assess RECIST v1.1 at screening. If required at baseline, MRI must be done prior to first dose of study treatment.

    20b. Every 6 cycles, MRI for tumor volume will be required throughout the study.

    20c. At EOT, MRI is only required if not performed within the past 3 months.

21. **Randomization:** Once all inclusion/exclusion (I/E) criteria have been confirmed, participants will be randomized to study treatment using the interactive response technology (IRT). Must be done prior to first dose of study treatment at baseline. Refer to Section 6.3.1 for more detail.

22. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles at study visits.

23. **Study treatment administration/diary:** First dose of study treatment (3 × 50 mg tablets) will be administered orally at the site at Cycle 1 Day 1 followed by a 2-hour observation period. Participants will administer study treatment at 150 mg (3 × 50 mg tablets) twice daily (BID) (approximately every 12 hours, without regard to food) continually in 28-day cycles throughout the study and record daily administration of each study treatment dose in the home ePRO device. Refer to Section 6.1 for more detail.

24. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, and the information can be obtained during the visit). Refer to Section 8.2.7 for more detail.

25. **AEs/Serious adverse events (SAEs):** Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail.

26. **Every 3 cycles and on:** Following Cycle 7 Day 1, participants will return every 3 cycles for study visits until death, progression of disease (confirmed by central review using RECIST v1.1), discontinuation of study treatment for any reason, study is stopped by the sponsor for any reason, or required number of PFS events have been observed and primary PFS analysis has been completed.

27. **End of treatment (EOT) visit:** Should be conducted prior to study treatment discontinuation or as close as possible to last dose of study treatment. Assessments may be conducted over a 2-day period but must be prior to unblinding (if applicable).

    Participants who experience disease progression (confirmed by central review using RECIST v1.1) will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (should be done within 14 days of disease progression confirmation).

    If participant discontinues study treatment for any other reason, the sponsor stops the study for any reason, or the required number of PFS events have been observed and the primary PFS analysis has been completed, the participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (should be done within 28 days of notification).

28. **Follow-up visit:** Only required for participants who are not continuing into the optional OLE phase and will occur 30 days (+7 days) after the last dose of study treatment.

1.3.2. Open-Label Extension Phase SoA

Cycle Number / Cycle Day	**Cycle 1 Day 1 Baseline[3]**	**Cycle 1[5] Day 8**	**Cycle 1[5] Day 15**	**Cycle 1[5] Day 22**	**Cycle 2[5] Day 1**	**Cycles 4, 7, 10 Day 1**	**Cycle 13 Day 1 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Visit Week (Calendar Day)	**Week 1 (Day 1)**	**Week 2 (Day 8)**	**Week 3 (Day 15)**	**Week 4 (Day 22)**	**Week 5 (Day 29)**	**Weeks 13, 25, 37 (Days 85, 169, 253)**	**Week 49 (Day 337) & On**		
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**See footnote 20**	**30 days (+7 days) after last dose**
Informed consent[1]	X								
I/E criteria[2]	X								
ECOG performance status[6]					X	X	X	X	X
Physical examination[7]		X[7a]	X[7b]	X[7b]	X[7b]	X[7a]	X[7a]	X[7a]	X[7a]
Vital signs[8]		X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X
12-lead ECG[9]	X[9a]	X[9b]	X			X	X	X	X
Laboratory									
Blood for PK sampling[10]	X[10a]	X[10b]							
Blood for clinical chemistry[11]	X[11a]	X	X	X	X	X	X	X	X
Urinalysis[12]		X				X	X	X	X
Monthly urine pregnancy test (WOCBP only)[13]						←==========	==========→	X	X
Patient-Reported Outcomes[14]									
BPI short form[14a]					←==========	==========	==========→		X
MDASI[14a]					←==========	==========	==========→		X
Desmoid-specific symptoms PRO assessment[14a]					←==========	==========	==========→		X
Desmoid-specific impacts PRO assessment[14b]					←==========	==========	==========→		X
PGIS[14b]					←==========	==========	==========→		X
PGIC[14b]					←==========	==========	==========→		X

Cycle Number Cycle Day	**Cycle 1 Day 1 Baseline[3]**	**Cycle 1[5] Day 8**	**Cycle 1[5] Day 15**	**Cycle 1[5] Day 22**	**Cycle 2[5] Day 1**	**Cycles 4, 7, 10 Day 1**	**Cycle 13 Day 1 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Visit Week (Calendar Day)	**Week 1 (Day 1)**	**Week 2 (Day 8)**	**Week 3 (Day 15)**	**Week 4 (Day 22)**	**Week 5 (Day 29)**	**Weeks 13, 25, 37 (Days 85, 169, 253)**	**Week 49 (Day 337) & On**		
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**See footnote 20**	**30 days (+7 days) after last dose**
Imaging									
Tumor imaging (CT or MRI) using RECIST v1.1[15]						X	X[15a] (then every 6 cycles)	X[15b]	
Enrollment and Study Treatment									
Enrollment/first dose of open-label study treatment[4]	X								
Study treatment dispensing[16]	X					X	X		
Study treatment administration/diary[17]	←==========						==========→		
Study treatment accountability		X	X	X	X	X	X	X	
Ongoing Monitoring									
Monthly wellness checks[18]	←==========						==========→		
ConMed review	←==========						==========→		
AE/SAE review[19]	←==========						==========→		

AE = adverse event; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; I/E = inclusion/exclusion; MDASI = MD Anderson symptom inventory; MRI = magnetic resonance imaging; OLE = open-label extension; PGIS = patient global impression of severity ; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = women of childbearing potential; v = version.

1. **Informed consent process:** Includes participant signing the ICF (exclusive to the OLE study phase) and must be conducted prior to first dose of open-label study treatment. Refer to Section 10.1.3 for more detail on the process.

2. **I/E criteria:** Exclusive to the OLE phase. Refer to Sections 6.7.2 and 6.7.3 for participant eligibility criteria specific to the OLE phase.

3. **Baseline visit:** The double-blind EOT visit will serve as the OLE baseline visit. All double-blind EOT visit assessments, as described in the double-blind SoA (Section 1.3.1), will be conducted prior to unblinding the participant's study treatment and prior to the first dose of open-label study treatment.

4. **Enrollment and first dose of open-label study treatment:** Participants will be enrolled in the OLE phase using the IRT only after all ongoing AEs/SAEs from the double-blind phase have been assessed for causality in a blinded manner by the investigator or qualified designee. All double-blind EOT visit assessments must be completed prior to unblinding and taking first dose of study treatment.

   Participants who were randomized to receive placebo in the double-blind phase will receive their first dose of study treatment at the site followed by a 2-hour observation period.

   Participants who were randomized to nirogacestat in the double-blind phase may take their first dose of open-label study treatment at home (observation period is not required).

5. **Cycle 1 (Day 8, 15 and 22) and Cycle 2 (Day 1):** Only applicable for participants who were previously randomized to receive placebo in the double-blind phase. If participant was randomized to receive nirogacestat in the double-blind phase, these study visits will not be conducted, and participants will begin with Cycle 4 assessments.

6. **ECOG performance status:** Refer to Section 10.8 for the ECOG scale.

7. **Physical examination:** Refer to Section 8.2.2 for more detail.

   7a. Complete physical examination required.

   7b. Brief physical examination required.

8. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature following at least 5 minutes of rest. Refer to Section 8.2.4 for more detail.

9. **12-lead ECGs:** Will be administered in triplicate (2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. ECGs should be performed after vital signs and prior to blood draws, when applicable. (Section 8.2.3)

   9a. At baseline, triplicate ECGs are required approximately 1-hour post-dose (open-label study treatment). Applicable only to participants who were previously randomized to receive placebo in the double-blind study phase.

   9b. At Cycle 1 Day 8 visit, triplicate ECGs are required 1-hour (±10 minutes) post-dose. Applicable to participants who were previously randomized to receive placebo in the double-blind study phase only.

10. **PK sampling:** Only applicable to participants who were previously randomized to receive placebo in the double-blind study phase. Refer to Section 8.5 and central laboratory manual for sample processing details.

    10a. At baseline, PK sampling is required at the following timepoints: pre-dose (prior to first dose of open-label study treatment) and 0.25, 0.5, 1, 1.5, and 2 hours post-dose. All efforts will be made to obtain within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing and will not be captured as a deviation if the exact time of the sample collection is noted on the source documents and eCRF.

10b. At Cycle 1 Day 8, participants will be instructed to **not** take their morning dose at home on the day of this visit. Instead, the morning dose will be taken at the site immediately following pre-dose PK sample.

11. **Clinical chemistry (hematology and serum chemistry):** Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details.

    11a. At baseline, blood draws for clinical chemistry will be done as part of the double-blind EOT visit (prior to unblinding). However, if clinical chemistry labs have not been conducted within the past 14 days prior to baseline, an additional blood draw will be required for same day local laboratory processing to reconfirm adequate organ and bone marrow function (refer to double-blind inclusion criteria 8) and must be done prior to first dose of open-label study treatment.

12. **Urinalysis:** Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results.

13. **Monthly urine pregnancy tests:** Only required for WOCBP. In between study visits, participants will administer home urine dipstick pregnancy tests and record the results in a home ePRO device (both are provided by the sponsor). Refer to Sections 8.2.6 and 10.4 for more detail.

14. **PROs:** Questionnaires should be completed before any other assessments/study procedures and before discussion of disease progression to avoid bias in the participant's responses to the questions. Participants will complete the PRO assessments using the home ePRO device monthly for the first year and then every 3 months thereafter during the OLE phase, and always prior to a study visit when applicable. The PROs will always be administered in this order: (1) BPI short form, (2) MDASI, (3) desmoid-specific symptoms PRO assessment, (4) desmoid-specific impacts PRO assessment, (5) PGIS, and (6) PGIC. (Section 8.1.2)

    14a. BPI short form, MDASI and desmoid-specific symptoms PRO assessment will be administered for 7 consecutive days (with a 24-hour recall period).

    14b. Desmoid-specific impacts PRO assessment, PGIS and PGIC will be administered on the last day of the 7-day PRO assessments noted in footnote 14a (with a 7-day recall period).

15. **Tumor imaging:** CT (contrast required unless contraindicated) or MRI (no contrast required) using RECIST v1.1 (modality to be determined by the investigator) is required. Whichever imaging modality is used to measure the tumor by RECIST v1.1 at screening in the double-blind phase must be used at each subsequent visit throughout the OLE phase. Scans will be submitted and reviewed centrally.

    15a. Scan is required every 3 cycles until Cycle 13 Day 1, and then every 6 cycles thereafter.

    15b. At EOT, scan is only required if not performed within the past 3 months.

16. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles during study visits.

17. **Study treatment administration/diary:** Participants will self-administer study treatment at 150 mg (3 × 50 mg tablets) BID (approximately every 12 hours, without regard to food), continually in 28-day cycles throughout the study and record daily administration of each study treatment dose in the home ePRO device. (Section 6.1):

18. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, and the information can be obtained during the visit). Refer to Section 8.2.7 for more detail.

19. **AEs/SAEs:** Will be monitored and documented from the time of informed consent and up to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail.

20. **End of treatment (EOT) visit:** Should be conducted prior to study treatment discontinuation or as close as possible to the last dose of study treatment. Assessments may be conducted over a 2-day period.

    Participants who experience disease progression (confirmed by central review using RECIST v1.1) will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (should be done within 14 days of disease progression confirmation).

    If participant discontinues study treatment for any other reason, the sponsor stops the study for any reason, or nirogacestat becomes commercially available, the participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (should be done within 28 days of notification).

21. **Follow-up visit:** Only required for participants who are not transitioning directly to commercial nirogacestat at time of discontinuation and visit will occur 30 days (+7 days) after the last dose of study treatment.

2. Introduction

Nirogacestat (PF-03084014) is a potent, small-molecule, selective, reversible, noncompetitive inhibitor of gamma secretase (GS). Nirogacestat is being investigated for the treatment of desmoid tumors/aggressive fibromatosis (DT/AF).

2.1. Study Rationale

The NIR-DT-301 Phase 3, double-blind, placebo-controlled study is being conducted to determine the efficacy and safety of nirogacestat in participants with progressing desmoid tumors. A Phase 1 solid tumor study provided preliminary efficacy (Messersmith, 2015), including long-term durable responses and safety of nirogacestat in desmoid participants (Villalobos, 2018). These encouraging results lead to a Phase 2 study in participants with progressing desmoid tumors (Kummar, 2017). This study demonstrated that nirogacestat resulted in a 29% response rate, significant tumor shrinkage as measured by magnetic resonance imaging (MRI) and no participants progressing while on therapy. Importantly, participants in the responder group had failed previous systemic therapies (imatinib or sorafenib) indicating a need for alterative therapeutic options for this patient population. These results support the further study of nirogacestat in this population.

2.2. Background

2.2.1. Desmoid Tumors/Aggressive Fibromatosis

Desmoid tumors, also referred to as aggressive fibromatosis, are rare, locally invasive, slow growing soft tissue tumors. According to the World Health Organization, desmoid tumors are defined as “clonal fibroblastic proliferations that arise in the deep soft tissue and are characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize” (Kasper, 2011). Desmoid tumors are considered benign; however, they cause significant morbidity by infiltrating or exerting mass effects on vital structures (Lewis, 1999; Smith, 2000). Desmoid tumors include soft tissue masses arising in any part of the body in different varieties of connective tissue, including muscle and fascia aponeurosis. The most common primary tumor sites include abdominal walls, limbs, girdles, and mesenteric areas. Desmoid tumors infiltrate surrounding structures and spread along plains and muscle, which can lead to severe pain, functional impairment, and more rarely, life-threatening conditions (Penel, 2017). Despite the benign nature of desmoid tumors, they can behave aggressively, causing significant morbidity, with elevated rates of local recurrence (as high as 60%) despite wide excisions (Penel, 2017). Mortality is occasionally observed owing to the local aggressive nature of some desmoid tumors that occur in the mesentery (Smith, 2000).

Desmoid tumors most commonly occur in individuals between the ages of 15 to 60 years, more often in young adults, with the peak age of about 30 years, and a 2- to 3-fold predominance in females (de Camargo, 2010; Skubitz, 2017). The incidence of desmoid tumors is about 2 to 4

cases per million per year in the general population, with fewer than 1000 cases diagnosed in the United States per year (Hosalkar, 2006).

The incidence of desmoid tumors is reported to be about 800- to 1000-fold higher in patients with familial adenomatous polyposis (FAP [Gardner Syndrome]), in which the adenomatous polyposis coli (APC) tumor suppressor gene is mutated (Skubitz, 2017). Familial adenomatous polyposis-associated desmoid tumor is more frequently associated with abdominal tumors, especially in the Gardner variant of FAP, which is associated with intestinal polyposis, osteomas, fibromas, and epidermal inclusion cysts (Skubitz, 2017). Intra-abdominal desmoid tumors are one of the leading causes of death in patients with FAP (Quintini, 2012). Although common in patients with FAP, most cases of desmoid tumors occur spontaneously in adults and are associated with a mutation in β-catenin (CTNNB1) (Lazar, 2008; Tejpar, 1999; Bo, 2012). β-catenin is an integral component of the Wnt/β-catenin/T-cell transcription factor signaling pathway, which is frequently dysregulated in cancer. Patients with desmoid tumors carrying β-catenin have a worse 5-year recurrence-free survival rate than patients with wild-type tumors (Kummar, 2017).

Histologically, desmoid tumors appear as poorly circumscribed proliferation of myofibroblastic cells with variable collagen deposition, and tumor margins are difficult to assess at the time of surgery. Desmoid tumors are morphologically heterogeneous and may exhibit striking morphological intratumoral and intertumoral heterogeneity (Skubitz, 2017). In some areas, tumors may resemble fibroblasts of inactive fibrous tissue, whereas other areas may resemble the active fibroblasts of wound healing.

The clinical course of desmoid tumor may be unusual and heterogeneous, characterized not only by tumor growth, proliferation, and disease progression, but also by stabilization and spontaneous remission (Kasper, 2011). Desmoid tumors can present almost anywhere throughout the body, and there are different factors by which desmoid tumors develop. They can have wide range of clinical symptoms, such as bloating, pain, or rectal bleeding, in the case of abdominal desmoid tumors; or extremity pain, decreased range of motion, and swelling, in the case of extremity desmoid tumors. Given the heterogeneity of desmoid tumor, predicting the desmoid tumor behavior and determining which treatment option is appropriate for a patient remains challenging.

2.2.2. Diagnosis

There are several guidelines published on diagnosis, treatment, and follow-up of participants with soft tissue sarcomas (STSs), including desmoid tumors. According to the clinical practice guidelines published in 2018 by the European Sarcoma Network Working Group, the basic principles for the diagnosis of STSs applies to desmoid tumors (Casali, 2018). Because of the ubiquitous nature of sarcomas and their site of origin, a multidisciplinary (e.g., radiologist, pathologist, surgeon, medical oncologist, etc.) approach to the diagnosis and management is warranted. Once a sarcoma mass is suspected, non-invasive imaging by MRI or computed tomography (CT) is performed. Additionally, a biopsy is performed, if feasible. Once the

primary diagnosis of desmoid tumor is confirmed, the potential treatment options outlined below are evaluated.

2.2.3. Treatment

Treatment options vary for each patient depending on the size, location and morbidity associated with the tumor. The wait-and-see policy is currently recommended as the first approach in desmoid tumors (Kasper, 2015). In a prospective study comparing surgical versus non-surgical approaches in primary desmoid tumors conducted by the French Sarcoma Group (Penel, 2017), the wait-and-see policy was implemented regardless of primary tumor location. For all patients, the 2-year event free survival (EFS) rate was 56%. The 2-year EFS was 63% and 70 % for patients managed by wait-and-see approach and for surgery with tumors in favorable locations (abdominal wall, intra-abdominal, breast, digestive viscera and lower limb), respectively. However, in patients with unfavorable tumor locations (chest wall, head and neck, upper limb) the 2-year EFS was significantly improved in participants initially managed with the wait-and-see approach (52%) vs surgery (25%). The authors concluded that the wait-and-see approach may be preferred to surgical resection.

Previously, surgery was the therapeutic option of choice for localized, extra-abdominal, small volume desmoid tumors. However, surgery is no longer regarded as the cornerstone of desmoid tumor treatment given the high rate of relapse after surgery, which exceeds 60% in larger studies, and the frequent observation of spontaneous disease regression and stabilization (Penel, 2017). Variables associated with local recurrence post-surgery include tumor location, age of the participant, and quality of the surgical resection (Kasper, 2011).

Radiotherapy has been used both in the adjuvant setting after surgery and in the primary setting, mainly for extra-abdominal tumors (Kasper, 2011). Radiotherapy after surgery is an independent positive prognostic factor for local recurrence and overall survival, and radiotherapy alone or in combination with surgery led to significantly lower recurrence rates (Kasper, 2011).

Modalities studied in clinical studies include: hormonal therapy since virtually all desmoid tumors express nuclear estrogen receptor-β, albeit at low receptor levels (Janinis, 2003); and nonsteroidal anti-inflammatory drugs, such as indomethacin and sulindac; however, limited responses have been observed with these agents.

In the case of unresectable, rapidly growing and/or symptomatic and/or life-threatening desmoid tumors, traditional chemotherapy may be considered. Kasper et al. (2011), provided an overview of chemotherapy regimens that have been studied in participants with advanced disease

For patients with relapsed or recurrent desmoid tumors, or for patients with desmoid tumors that are not amenable to surgery or radiotherapy, or if surgery is potentially mutilating, various systemic therapy have been studied, although little in controlled clinical studies. Schöffski et al conducted a survey of physician's preference for systemic treatment for patients with advanced desmoid tumors using a structured questionnaire (Schöffski, 2018). Results indicated that disease progression and failure of local therapy were typical indications for the use systemic therapy.

Thus, clinical studies with systemic agents should ideally select a homogenous population with advanced, progressive, and symptomatic desmoid tumors and/or functional impairment after failure of observation only strategies and/or local treatments such as surgery or radiotherapy. Due to the spontaneous regression observed in participants with desmoid tumors, studies should ideally be randomized, with physician's choice or placebo as potential comparators.

Meaningful responses have been observed with tyrosine kinase inhibitors, such as imatinib (Kasper, 2017) and sorafenib. Recently, the results from a Phase 3 study of sorafenib compared to placebo were presented at the American Society of Clinical Oncology conference in June 2018 (Gounder, 2018). The study enrolled 87 participants with either symptomatic or unresectable progressive desmoid tumors that were randomized 2:1 to sorafenib (n=50) or placebo (n=37). The median PFS for placebo was 9.4 months (95% CI [5.7, not evaluable]) and was not reached for sorafenib (HR = 0.14, 95% CI [0.06, 0.33], p<0.0001). The objective response rate (ORR) for sorafenib was 33% and for placebo was 21%, p = 0.3. Spontaneous regressions are known to occur in desmoid participants. This study confirmed the need for a control group (Schöffski, 2018) in desmoid tumor clinical studies particularly given the spontaneous response rate in the placebo group.

Additional targeted agents such as sirolimus and pazopanib are also being studied in participants with desmoid tumors (NCT01265030 and NCT01876082, respectively).

2.2.3.1. Clinical Studies with Nirogacestat

2.2.3.1.1. Study A8641014A: Phase 1 study of PF-03084014 in participants with advanced solid tumor malignancy and T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma

Messersmith and colleagues conducted a Phase 1, dose-finding study to determine the maximum tolerated dose (MTD), the recommended Phase 2 dose (RP2D), and to evaluate safety of continuous administration of nirogacestat in participants with advanced solid tumors (Messersmith, 2015). Sixty-four participants received doses of nirogacestat and the MTD was determined to be 220 mg, administered twice daily (BID). The RP2D was determined to be 150 mg BID, given comparable NOTCH related target inhibition. The most common reason for discontinuation from nirogacestat was objective progression or relapse of disease (32 participants). The most common primary diagnosis was desmoid tumor (9 participants), with a mean duration since diagnosis of 7.7 years. All participants received surgeries and about half of the participants received radiation therapy. The majority (60 [93.8%] participants) received previous systemic therapies and more than half (35 [54.7%] participants) had systemic therapies for >3 regimens.

Of the 64 participants with solid tumors, 62 experienced at least 1 adverse event (AE), and 54 experienced at least 1 treatment-related AE (1 participant with a Grade 1 AE of upper respiratory infection was excluded from the analysis due to a database error). The most common treatment-related AEs were diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite. The majority of these AEs were Grade 1 to Grade 3. Dose reductions due to treatment-related AEs were infrequent and were reported in 9 (14%) participants at various times

during treatment (from Cycle 1 to Cycle 10). Across dose levels, 5 (7.8%) participants had Grade 2 or Grade 3 diarrhea that resolved with dose reduction. Temporary discontinuation occurred in 21 (32.8%) participants, 13 (20.3%) of which were for a treatment-related AE. All treatment-related AEs that led to temporary discontinuation (diarrhea, hypophosphatemia, rash, nausea, vomiting, and fatigue) or dose reduction were Grade 1 to Grade 3, and most resolved following temporary discontinuation or dose reduction. Seven (10.9%) participants permanently discontinued treatment primarily owing to an AE; of these, 4 (6.3%) participants discontinued for a treatment-related AE: one each for Grade 4 anaphylactic shock (100 mg BID) (an event thought to be related to co-administration of IV morphine), Grade 1 visual impairment (150 mg BID), Grade 3 drug hypersensitivity (220 mg BID), and Grade 3 rash (330 mg BID). The hypersensitivity reaction (rash associated with chest tightening and shortness of breath) resolved with intravenous steroid therapy after discontinuation of study treatment.

There were 46 participants with solid tumors evaluable for response. Overall, ORR was 13.0% (95% CI [94.9, 26.3]) for these participants. Six participants had an ORR with 1 complete response (CR) (participant with thyroid cancer) and 5 partial responses (PRs). All 5 PRs were reported by participants with desmoid tumors, who accounted for 71.4% (95% CI [29.0, 96.3]) of the 7 participants with desmoid tumors evaluable for response. At the time of data cutoff, all 6 responders were censored in the calculation of duration of response. All 5 responders with desmoid tumors had not progressed and were censored at the time of data cutoff, with 4 still on study and 1 discontinued due to noncompliance. The participant with thyroid cancer with CR later had recurrence of disease but was censored at the last disease assessment of CR due to missed tumor assessments.

Overall, nirogacestat was well tolerated with an MTD determined to be 220 mg BID and a RP2D to be 150 mg BID. The best tumor responses were 5 PRs out of 7 evaluable participants with desmoid tumors.

Villalobos and colleagues reported the long-term follow-up of the 7 participants with desmoid tumors from the Phase 1 study (Villalobos, 2018). As previously described, 5 of the 7 participants with desmoid tumors had a PR with a mean time to response of 11.9 months. All participants that achieved a PR continued to maintain response between 48 and 73+ months. Four participants who discontinued therapy remained free of progression between 11 and 53+ months. One participant had a PFS of >42 months, with a 17% decrease in the target lesion. Prolonged disease control was observed for 6 out of 7 of the participants with desmoid tumors treated with nirogacestat.

2.2.3.1.2. National Cancer Institute Protocol 14-C-0007: Phase 2 study of gamma secretase inhibitor PF-03084014 in adults with desmoid tumors/aggressive fibromatosis (NCT01981551)

A Phase 2 study was conducted by Investigators at the National Cancer Institute (NCI) to evaluate the ORR after therapy with nirogacestat in participants with recurrent, refractory, progressive desmoid tumors (Kummar, 2017). Seventeen participants received daily doses of nirogacestat at 150 mg BID continuously in 3-week cycles. Response to treatment was evaluated

at Cycle 1 and every 6 cycles (18 weeks) thereafter by Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1. Of the 17 participants treated in the study, 15 had mutations in APC or CTNNB1 genes. Sixteen participants were evaluable for response; 5 participants experienced a confirmed PR and had been on study for more than 2 years, and the remaining 11 participants had stable disease. No participant progressed on study. The AE profile was consistent with previous reports (Messersmith, 2015) and consisted of all participants experiencing at least 1 Grade 1 or Grade 2 AE; and the most commonly reported AEs were diarrhea and skin disorders. Four participants had a dose reduction while on study. Two participants received a reduced dose of 100 mg BID as a result of persistent Grade 3 nausea and diarrhea, 1 participant developed urticaria nonresponsive to dose reduction and came off study, and 1 participant developed a Grade 2 maculopapular rash, which resolved with dose reduction. The only Grade 3 AE attributable to study treatment was hypophosphatemia, reported in 8 participants, and is a known class effect of GS inhibitors.

2.3. Rationale for Nirogacestat in Desmoid Tumors

Emerging evidence in recent years presents the Notch pathway as a promising target for treatment of solid tumors. It has been reported that aberrant Notch activation and deregulated expression of Notch ligands and targets are associated with a broad panel of solid tumors. At least 3 Notch members (NOTCH1, 3, and 4) have been found to be involved in solid tumors.

The molecular mechanism for the oncogenic activity of Notch intracellular domain (NICD) may include inhibiting differentiation, promoting survival, or accelerating proliferation. Potential oncogenic targets of NOTCH1 include Myc, cyclin D1, and several other factors. In the case of Myc, evidence demonstrates that Myc is a direct target gene of Notch 1 and essential for development of both T-cell leukemia and mammary tumors in mice (Sharma, 2006; Klinakis, 2006).

Recent studies suggest crosstalk between the Wnt and Notch pathways (Rodilla, 2009; Rampazzo, 2013). It has been shown that Notch activity is increased in colorectal cancer cells through upregulation of JAG1 mediated by β-catenin, and levels of hairy and enhancer of split-1 (Hes1) messenger ribonucleic acid are significantly upregulated in APCmin/+ mouse intestinal cancer models (Ungerback, 2011). Expression of NOTCH1 and Hes1 have been observed in mesenchymal stromal cells found in desmoid tumor, suggesting that the Notch pathway is possibly related to desmoid tumorigenesis (Shang, 2015). Importantly, nirogacestat has been shown to inhibit the Notch pathway in desmoid tumors by inhibiting NICD and Hes1 expression and this blockade results in grow arrest rather than apoptotic cell death in desmoid tumors (Shang, 2015).

This collective data suggests that Notch signaling plays an important role in cancer development. Hence, inhibition of Notch signaling is an important strategy for therapeutic treatment.

2.4. Rationale for Participant Population and Placebo Arm

Desmoid tumors most commonly occur in individuals between the ages of 15 to 60 years, more often in young adults, with the peak age of about 30 years, and a 2- to 3-fold predominance in females (de Camargo, 2010; Skubitz, 2017). This Phase 3 study will enroll participants ≥18 years old. The pharmacokinetics (PK) and optimal dosing of nirogacestat in younger participants has not been established. A future study in pediatric participants is planned.

There is no FDA-approved therapeutic option for the treatment of desmoid tumors, nor is there an accepted standard of care for patients with advanced progressing tumors. The population will be assessed by a wait-and-see approach and depending on the tumor growth and location, different therapeutic options may be considered. The recently analyzed Phase 3 study of sorafenib versus placebo (Gounder, 2018) showed a significant improvement in PFS in the sorafenib arm, but also demonstrated responses in the placebo group highlighting the need for this control in Phase 3 studies.

2.5. Benefit/Risk Assessment

To date, the safety profile of single-agent nirogacestat in participants with advanced cancer has been characterized by manageable and reversible toxicities. The most frequently reported AEs were diarrhea, fatigue, nausea, vomiting, hypophosphatemia, cough, and rash. The majority of the events were mild-to-moderate in intensity. Additionally, a Phase 2 (investigator-initiated) study in adult participants with desmoid tumors showed a similar AE profile (Kummar, 2017). All participants in the study experienced at least one Grade 1 or Grade 2 AE; with the most commonly reported events being diarrhea and skin disorders. Based on the mechanism of action and nonclinical/clinical study data, the important identified risks associated with nirogacestat administration include notch-related effects on hematopoietic (immune) function, notch-related effects on gastrointestinal function, skin rash, and hypophosphatemia. Important potential risks include effects on the hepatic system, including potential liver cholestasis. These risks will be assessed. Additionally, risk measures are in place to minimize potential risks to study participants, and review of safety data will be conducted on an ongoing basis in order to identify new safety signals that may arise during the program.

The results of the nonclinical toxicology and safety pharmacology studies, together with the clinical experience in participants with advanced cancers (Sections 2.2.3.1.1 and 2.2.3.1.2), support the hypothesis that nirogacestat may represent an important therapeutic approach in patients with desmoid tumors. Thus, the projected benefit/risk balance is considered favorable for further development in this patient population.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirogacestat may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
To determine the efficacy (as defined by PFS) of nirogacestat in adult participants with progressing DT/AF.	PFS defined as the time from randomization until the date of assessment of progression or death by any cause will be determined using RECIST v1.1 (Eisenhauer, 2009; Section 10.9). The documented date of progression will be determined by an independent, blinded, central radiologic review.
Secondary	**Secondary**
To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of AEs;	Safety endpoints will include incidence of treatment-emergent AEs, changes in laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs). Tolerability will be assessed according to toxicities graded by NCI Common Terminology Criteria for Adverse Events v5.0;
To determine the overall response rate (CR + PR) of nirogacestat in participants with progressing DT/AF;	Overall response rate, defined as the proportion of participants with CR + PR assessed by RECIST v1.1 criteria;
To determine the duration of response;	Duration of response for participants whose best response is CR or PR;
To compare tumor volume changes measured by MRI in participants with progressing DT/AF; and	Change in tumor volume from baseline as assessed by MRI volumetric; and
To evaluate desmoid tumor symptoms and impacts using patient-reported outcomes (PROs).	Symptoms and impacts will be assessed by evaluating change from baseline on the desmoid-specific PRO assessment, MDASI, and BPI short form.

Objectives	**Endpoints**
Exploratory	**Exploratory**
To evaluate desmoid tumor symptoms and impacts using PROs;	Symptoms and impacts will be assessed by evaluating changes using the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC);
To perform genotyping for germline and somatic mutation in APC and CTNNB1 genes;	Assess the frequency and distribution of each mutation;
To assess modulation of the Notch pathway by evaluating NOTCH response genes in tumor biopsies at screening and disease progression or end of treatment (EOT);	Change in expression pre- and post-dose on Notch pathway genes;
To assess MRI T2 hyperintensity at baseline and post-drug administration;	Assess the percent change in MRI T2 intensity;
To inform development of a population PK model of nirogacestat; and	To optimally collect sparse PK samples to increase precision of model parameters; and
To evaluate the effect of nirogacestat on clinical events related to disease specific desmoid tumor co-morbidity.	Summarize the incidence and frequency of events which may include hospitalization due to small bowel obstruction, hospitalization due to desmoid tumor-related pain, surgery for desmoid tumor.

4. Study Design

4.1. Overall Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. Approximately 94 eligible participants will be randomized to study treatment (nirogacestat or placebo) in a 1:1 ratio. Randomization will be stratified by primary tumor location.

This study will consist of 2 phases: the double-blind phase and the optional open-label extension (OLE) phase. Refer to the schedule of activities (SoA; Sections 1.3.1 and 1.3.2) for details on assessments and timing of study visits.

Refer to Section 1.2 for the study schema.

4.1.1. Overall design for the double-blind phase:

Participants will be screened up to 28 days prior to the first dose of study treatment and participant eligibility will be based on inclusion and exclusion criteria described in Sections 5.1 and 5.2. Participants will be randomized to study treatment at Cycle 1 Day 1 using interactive response technology (IRT), and will orally administer 150 mg BID, continually in 28- day cycles.

Participants will remain in the double-blind phase until:

- Participant experiences death;
- Participant experiences disease progression (confirmed by central review using RECISTv1.1), and at this time participant will be unblinded and have the option to enter the OLE phase if eligible (Section 6.7.1);
- Participant prematurely discontinues study treatment in the study for any reason;
- The study is stopped by the sponsor for any reason; or
- The required number of PFS events have been observed and the primary PFS analysis has been completed (based on current statistical assumptions, this is anticipated to be approximately 2 years after the first participant is randomized). Participants will be unblinded and have the option to enter the OLE phase at this time.

4.1.2. Overall design for the optional OLE phase:

The OLE phase is applicable to eligible participants (refer to Sections 6.7.2 and 6.7.3 for the OLE phase eligibility criteria). Participants will orally administer 150 mg open-label study treatment (nirogacestat) BID continuously in 28-day cycles.

Participants will remain in the OLE phase until:

- Participant experiences death;

- Participant experiences disease progression (confirmed by central review using RECIST v1.1);
- Participant prematurely discontinues study treatment for any reason;
- The study is stopped by the sponsor for any reason; or
- Nirogacestat is commercially available.

4.2. Scientific Rationale for Study Design

Based on the promising, prolonged tumor responses and overall tolerability with nirogacestat observed in the Phase 1 and Phase 2 studies, this Phase 3 double-blind, placebo-controlled study is being proposed to determine the efficacy and safety in participants with unresectable, recurrent or relapsed progressing desmoid tumors. Progression-free survival was selected as the primary endpoint based on the previous clinical studies with nirogacestat in desmoid participants with progressing tumors and the observation that only one participant progressed after 15 months on therapy (1 out of 24 participants) (Villalobos, 2018 and Kummar, 2017). The rate of progression in untreated desmoid patients is about 9 months (Gounder, 2018). A placebo group was chosen because of the known spontaneous regressions that can occur with desmoid tumors. Progressing desmoid tumors can be unrelenting to patients particularly when they are unresectable or unresponsive to systemic treatment and halting progression, particularly when paired with tumor shrinkage, is a significant outcome for patients. Because of the size and location of desmoid tumors they can often be associated with pain, loss of range of motion, and impact on daily living. This study incorporates outcome tools to assess change from baseline in these outcome measures, as changes in pain, for example, have been observed in participants treated with nirogacestat that had significant tumor shrinkage (Kummar, 2017).

4.3. Justification for Dose

An open-label, non-randomized, Phase I dose finding study (Messersmith, 2015) in participants with advanced solid tumors was conducted to determine the MTD and recommended phase 2 dose (RP2D) for future clinical development of nirogacestat. In the dose-finding portion of the study, the MTD of nirogacestat administered BID continually for 21 days was established at 220 mg BID in participants with advanced solid tumors. Additional participants were subsequently enrolled in the expansion cohort at 150 mg or 220 mg BID. The RP2D in participants with advanced solid tumors was determined to be 150 mg BID by comparing the tolerability, PK, and pharmacodynamic profile of nirogacestat at these 2 doses. At a dose level of 150 mg BID, the most frequently reported AEs were diarrhea (70%), fatigue (44%), nausea (39%), decreased appetite (26%), vomiting (26%), and hypophosphatemia (22%). Analysis of whole blood samples demonstrated that HES4 showed the most consistent PD response, with a greater than 2-fold down-modulation observed in 17 of 19 evaluable participants with solid tumors. Additionally, in participants with advanced desmoid tumors, there appeared to be a clear response to nirogacestat treatment. Nirogacestat was also investigated as a single agent in a Phase 2 study in 19 participants with triple-negative breast cancer at the RP2D of 150 mg BID.

Neither efficacy nor PK were summarized for this study, but the AE profile was consistent with the Phase 1 study. Lastly and importantly, nirogacestat at 150 mg BID was studied in another Phase 2 study conducted by the NCI in participants with progressing desmoid tumors (Kummar, 2017). In this study, nirogacestat activity was established with 5 PR (29%) out of 16 evaluable participants. The dose of 150 mg BID was chosen for this Phase 3 clinical study based on the safety profile at this dose as well as the encouraging tumor responses in participants with desmoid tumors.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3) (including telephone contact) for the last participant in the study globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

These criteria are for the double-blind phase of the study only. The inclusion criteria for the OLE phase can be found in Section 6.7.2.

Participants are eligible to be included in the double-blind phase only if all the following criteria apply:

Age

1. Participant must be at least 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participant has DT/AF that has progressed by ≥20% as measured by RECIST v1.1 within the 12-month period prior to first dose of study treatment.
3. Participant has:
    a. Newly diagnosed, measurable progressing DT/AF that is not amenable to surgical resection or radiation therapy;

    OR

    b. Recurrent, progressing DT/AF following CR to initial therapy;

    OR

    c. Preexisting DT/AF and has previously received therapy and the residual tumor has progressed.
4. Participant agrees to provide archival or new tumor tissue for confirmation of disease.
5. If participant was previously treated with an investigational therapy for treatment of DT/AF, participant must have completed prior therapy at least 28 days prior to signing informed consent. All toxicities from prior therapy must resolve to ≤Grade 1 or baseline.
6. Participants who are receiving nonsteroidal anti-inflammatory drugs (NSAIDs) as treatment for conditions other than DT/AF must be receiving them for:
    a. Chronic scheduled daily use (defined as stable for 28 days prior to signing informed consent); or
    b. Occasional use (defined as ≤3 days per week) for the treatment of pain or as an anti-inflammatory in licensed conditions such as headache, arthritis, etc.

7. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 at screening (refer to Section 10.8 for ECOG performance status scale).
8. Participant has adequate organ and bone marrow function as defined by the following Screening laboratory values:
    a. Absolute neutrophil count ≥1500/µL;
    b. Platelets ≥100 × 10^3/µL;
    c. Hemoglobin ≥9 g/dL;
    d. Total bilirubin ≤1.5 × upper limit of normal (ULN) (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%);
    e. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase) ≤2 × ULN; and
    f. Creatinine ≤1.5 × ULN or if creatinine >1.5 × ULN then calculated creatinine clearance should be ≥60 mL/min/1.73 m^2 (using the Cockcroft-Gault formula);
9. Participant can swallow tablets and has no gastrointestinal conditions affecting absorption.

Sex

10. Male or Female

    Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. **Male participants:**
Male participants are eligible to participate if they agree to the following during the treatment period and for at least 90 days after the last dose of study treatment:

- Refrain from donating sperm;

  PLUS either**:**

- Be abstinent from sexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent;

  OR

- Must agree to contraception/barrier as detailed below:
    - Agree to use a double-barrier contraception method when having sexual intercourse with a woman of childbearing potential (WOCBP). Refer to Section 10.4 for definition of a WOCBP.

b. **Female participants:**
A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP.

OR

- Is a WOCBP and using 2 contraceptive methods that are highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.4 during the treatment period and for at least 30 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during the treatment period and for at least 60 days after the last dose of study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at the baseline visit prior to the first dose of study treatment.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

11. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

These criteria are for the double-blind phase only. The exclusion criteria for the OLE phase can be found in Section 6.7.3.

Participants are excluded from the double-blind phase if any of the following criteria apply:

Medical Conditions

1. Participant has known malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of nirogacestat (e.g., gastric bypass, lap band, or other gastric procedures); delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.
2. Participant has experienced any of the following within 6 months of signing informed consent: clinically significant cardiac disease (New York Heart Association Class III or IV), myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism.
3. Participant has abnormal QT interval corrected by Fridericia's formula (>450 msec for male participants, >470 msec for female participants, or >480 msec for participants with

bundle branch block) after electrolytes have been corrected (triplicate ECG readings, done 2-3 minutes apart and averaged) at screening.

4. Participant has congenital long QT syndrome.
5. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
6. Current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones).

Prior/Concomitant Therapy

7. Participant previously received or is currently receiving therapy with GS inhibitors or anti-Notch antibody therapy.
8. Participant is currently using or anticipates using a tyrosine kinase inhibitor within 28 days prior to the first dose of study treatment.
9. Participant is currently using or anticipates using food or drugs that are known strong/moderate cytochrome P450 3A4 (CYP3A4) inhibitors (Section 10.7) within 14 days prior to the first dose of study treatment.
10. Participant is currently using or anticipates using food or drugs that are known strong CYP3A4 inducers within 14 days prior to the first dose of study treatment.
11. Participant is currently using or anticipates using chronic daily NSAIDs for treatment of DT/AF within 14 days prior to the first dose of study treatment.

Prior/Concurrent Clinical Study Experience

12. Participant is currently enrolled or was enrolled within 28 days of signing informed consent in another clinical study with any investigational drug or device; however, participation in observational studies is permitted.

Diagnostic assessments

13. Participant has a positive human immunodeficiency virus antibody test.
14. Participant has presence of Hepatitis B surface antigen at screening.
15. Participant has a positive Hepatitis C antibody or Hepatitis C ribonucleic acid (RNA) test result at screening or within 3 months prior to starting study treatment.

    NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

    Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

Other Exclusions

16. Participant is unable to tolerate MRI or for whom MRI is contraindicated.
17. Participant with active bacterial, fungal, or viral infection including but not limited to the use of antibiotics, antifungals, or antiviral agents at the time of screening.
18. Participant has experienced other severe acute or chronic medical or psychiatric conditions, including recent (within 1 year of signing informed consent) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

5.3. Lifestyle Considerations

1. No specific lifestyle restrictions are required in this study.
2. Study treatment may be taken without regard to food.
3. Refer to Section 6.5 for more detail on concomitant therapy including exclusions and restrictions.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at any time and do not need to wait the full 28 days of the screening period. There is no set limit to how many times a participant may be rescreened if the investigator considers the rescreening medically and scientifically appropriate. Rescreened participants will be assigned a new participant number at the time of rescreening using IRT.

6. Study Treatment

Study treatment for this study is defined as an investigational treatment (nirogacestat or placebo) intended to be administered to a study participant according to the study protocol.

6.1. Study Treatment(s) Administered

- Participants will be instructed to swallow tablets whole and not to chew them prior to swallowing.
- No tablet should be ingested if it is broken, cracked, or otherwise not intact.
- Participants should take their dose BID orally, approximately every 12 hours, without regard to food.
- Participants will be instructed to record their daily administration of each study treatment dose in a home electronic patient report outcome (ePRO) device, which will be provided by the sponsor.
- Delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.

Table 2 Study Treatments Administration

ARM Name	Experimental	Control
Treatment Name	Nirogacestat	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	50 mg	50 mg
Dosage Level(s)	150 mg BID	150 mg BID
Route of Administration	Oral	Oral
Sourcing	Sponsor will provide sites with study treatment for individual participant distribution	Sponsor will provide sites with study treatment for individual participant distribution
Packaging and Labeling	Study treatment will be provided in 90 count bottles. Each bottle will be labeled as required per country requirement	Study treatment will be provided in 90 count bottles. Each bottle will be labeled as required per country requirement

Former Name	PF-03084014	Not Applicable

6.1.1. Double-Blind Phase Dosing Administration

Once the informed consent process (Section 10.1.3) for the double-blind phase has been conducted, all entry criteria have been met, and the randomized treatment assignment confirmed using IRT, the first dose of double-blind study treatment (3 × 50 mg tablets) will be administered at the site followed by a 2-hour observation period. Throughout the double-blind phase, participants will administer 150 mg (3 × 50 mg tablets) of study treatment BID (approximately every 12 hours, without regard to food), continually in 28-day cycles.

6.1.2. Open-Label Phase Dosing Administration

If a participant is eligible to enter the OLE phase, open-label study treatment will **not** be administered until all EOT visit assessments from the double-blind phase have been completed and participant has signed the ICF specific to the OLE phase. All ongoing AEs/SAEs from the double-blind phase must be assessed for causality by the investigator or qualified designee and recorded in the electronic case report forms (eCRFs) prior to enrolling in the OLE phase using the IRT.

Participants who were randomized to receive placebo in the double-blind phase will receive their first dose of study treatment at the site followed by a 2-hour observation period.

Participants who were randomized to nirogacestat in the double-blind phase may take their first dose of open-label study treatment at home. An observation period at the site is not required.

Throughout the OLE phase, participants will administer 150 mg (3 × 50 mg tablets) of study treatment BID (approximately every 12 hours, without regard to food), continually in 28-day cycles.

6.1.3. Study Treatment Errors

Study treatment errors may result in this study from the administration or consumption of the wrong study treatment, by the wrong participant, at the wrong time, or at the wrong dosage strength. Such study treatment errors occurring to a study participant are to be captured on the AE page of the eCRF and on the SAE form when appropriate. In the event of a dosing error, the sponsor should be notified immediately.

Study treatment errors are reportable irrespective of the presence of an associated AE/SAE, including errors involving participant exposure to the product.

Whether or not the study treatment error is accompanied by an AE (as determined by the investigator), the study treatment error (if applicable), and any AE(s), must be captured on an AE eCRF page.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment shipments received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants randomized in the IRT may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment (bottles/tablets) are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

- All participants will be centrally assigned to randomized study treatment (nirogacestat or placebo) using the IRT.
- Randomization will be stratified based on either favorable (abdominal wall, breast, intraabdominal and lower limb) or unfavorable (chest wall, head and neck and upper limb) tumor location. The tumor location used for stratification should be the same as the reported target lesion used for assessment of the primary endpoint.
- The IRT will assign the participant number at screening and that number will be utilized for the duration of the study. Before the study is initiated at a site, instructions and log-in information for the IRT will be provided to appropriate site personnel.
- Study treatment will be dispensed to participants every 3 cycles during study visits as described in the SoA (Section 1.3).
- Returned study treatment will not be re-dispensed to the participants.

6.3.2. Blinding

For the double-blind phase, the participant, investigator, and all other clinical site personnel will be blinded to the assigned treatment allocation. All sponsor personnel will also be blinded except for the sponsor's quality assurance designee(s), safety designee(s), and clinical supply material designee(s).

6.3.2.1. Breaking the Blind

Sites will be provided instructions on how to break the blind in the IRT prior to study initiation. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor prior to unblinding a participant's study treatment assignment unless this could delay emergency treatment of the participant. Refer to Section 11.1.3 for the medical monitor contact details.

If a participant's study treatment assignment is unblinded, the sponsor or medical monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

The blind is not to be broken during the double-blind phase of the study unless:

- Considered necessary by the investigator for emergency situations as noted above;
- The participant has confirmed progressive disease (confirmed by central review using RECIST v1.1); or
- All required number of PFS events have been observed and the primary PFS analysis has been completed.

Unblinding at the clinical site for any other reasons during the double-blind phase will be considered a protocol deviation.

6.4. Study Treatment Compliance

Participant compliance with study treatment will be assessed at each visit. Compliance will be assessed by counting returned tablets and reviewing the dosing diary entries from the home ePRO device (participants will be trained on the home ePRO device at the screening visit). At each study visit, any discrepancies will be discussed with the participant and will be recorded in the source documentation. The number of tablets dispensed, and the number of tablets returned will be recorded in the eCRF, as well as any deviations. In the case of an overdose, refer to Section 8.4 for instructions.

6.5. Concomitant Therapy

6.5.1. Prior Concomitant Medications and/or Procedures

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of informed consent and receives during the study must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates; and

- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy. Refer to Section 11.1.3 for the medical monitor contact details.

6.5.1.1. Known Drug Interactions

6.5.1.1.1. Cytochrome P450 Inhibitors and Inducers

Because inhibition of CYP3A4 isoenzymes may increase nirogacestat exposure leading to potential increases in toxicities, the use of known strong/moderate CYP3A4 inhibitors (Section 10.7) is not allowed throughout the double-blind and OLE study phases and must be stopped at least 14 days prior to the first dose of double-blind study treatment.

Nirogacestat metabolism may be induced when taking strong CYP3A4 inducers resulting in reduced plasma concentrations. Therefore, co-administration of nirogacestat in combination with strong CYP3A4 inducers (Section 10.7) is not allowed throughout the double-blind and OLE study phases and must be stopped at least 14 days prior to the first dose of double-blind study treatment.

6.5.1.1.2. Anti-Emetic and Anti-Diarrheal Therapy

The choice of anti-emetic drug(s) and anti-diarrheal drug(s), as well as the duration of treatment, is up to the investigator assuming there is no known or expected drug-drug interaction (DDI) (Section 10.7). If a DDI is expected, then the drug(s) use must be approved by the medical monitor.

6.5.1.1.3. Other Concomitant Therapy

Nonclinical studies have indicated that nirogacestat is a substrate for the drug efflux transporter P-glycoprotein (P-gp). Therefore, caution should be used when co-administering the study treatment with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, elacridar, erythromycin, felodipine, itraconazole, mibefradil, nifedipine, nitredipine, quinidine, ranolazine, talinolol, valspodar, and verapamil or strong P-gp inducers such as rifampin and St. John's Wort.

6.5.1.2. Excluded Concomitant Medications and/or Procedures

Table 3 describes the concomitant medications and/or procedures that are excluded/restricted prior and/or throughout the duration of the study.

Table 3 Restricted/Excluded Medications and/or Procedures

Medication/Procedure	Exclusion Timeframe
Chronic daily use of NSAIDS for treatment of DT/AF	Use within 14 days prior to first dose of double-blind study treatment and throughout

Medication/Procedure	**Exclusion Timeframe**
	the duration of the double-blind and OLE phases
Strong/moderate CYP3A4 inhibitors (Section 10.7)	Use within 14 days prior to first dose of double-blind study treatment and throughout the duration of the double-blind and OLE phases
Strong CYP3A4 inducers (Section 10.7)	Use within 14 days prior to first dose of double-blind study treatment and throughout the duration of the double-blind and OLE phases
Tyrosine kinase inhibitors	Use within 28 days prior to first dose of double-blind study treatment and throughout the duration of the double-blind and OLE phases
GS inhibitors	Prior or current use
Anti-Notch antibody therapy	Prior or current use
Gastric bypass, lap band, or other gastric procedures	Not allowed
Delivery of nirogacestat via nasogastric tube or gastrostomy tube	Not allowed
Enrollment in another clinical study with any investigational drug or device	Within 28 days prior to signing ICF

Participants who are receiving NSAIDs as treatment for conditions other than DT/AF must be receiving them for chronic scheduled daily use (defined as stable for 28 days prior to signing informed consent and must remain stable throughout the double-blind phase of the study) or occasional use (defined as ≤3 days per week) for the treatment of pain or as an anti-inflammatory in licensed conditions such as headache, arthritis, etc.; dose increases will not be permitted during the double-blind and OLE phases of the study.

6.5.1.3. Supportive Care

6.5.1.3.1. Phosphate Supplements

Nirogacestat has been associated with hypophosphatemia which may require phosphate supplementation. The choice of phosphate replacement, as well as the duration, is at the investigator's discretion.

6.6. Dose Modification

Every effort should be made to administer study treatment at 150 mg BID; however, in the event of significant toxicity, dosing may be interrupted and/or dose reduced as described in Table 4.

Interruption of study treatment should continue until the toxicity is resolved to ≤Grade 1 or baseline. A delay of study treatment for more than 14 days due to any toxicity may require permanent discontinuation. After 14 days of interruption, study treatment may be resumed only after discussion with the medical monitor and approval by the sponsor. Refer to Section 11.1.3 for the medical monitor contact details.

After interruption, doses of study treatment may be resumed at a reduced dose of 100 mg BID. If the same toxicity does not recur within 14 days, study treatment can resume to 150 mg BID. Should the same ≤Grade 3 toxicity recur at 100 mg BID, and the toxicity is considered related to the study treatment, study treatment may be discontinued following discussion with the medical monitor and sponsor.

An unscheduled visit may be performed at any time during the study. Assessments to be performed at the unscheduled visit will be determined by the investigator.

Table 4 Dose Modifications or Interruptions for Selected Toxicities

Toxicity (NCI CTCAE)	**Study Treatment Dosing**
Gastrointestinal Toxicities	
Grade ≥3 diarrhea persisting for ≥3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Grade ≥3 nausea persisting for ≥3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Grade ≥3 vomiting persisting for ≥ 3 days despite maximal medical therapy	Decrease does to 100 mg BID
Other toxicities	
Grade ≥3 skin toxicity	Decrease dose to 100 mg BID

Toxicity (NCI CTCAE)	**Study Treatment Dosing**
Grade ≥3 hypersensitivity reaction	Permanently discontinue
Grade ≥3 hypophosphatemia persisting for ≥7 days despite maximal replacement therapy and in the absence of symptoms	Decrease dose to 100 mg BID
Other Grade ≥3 non-hematological toxicities	Decrease dose to 100 mg BID
Grade ≥3 hematological toxicities	Decrease dose to 100 mg BID; Second episode: Permanently discontinue
Hepatic toxicities	Refer to Section 7.1.1

6.7. Treatment after the End of the Study

6.7.1. Optional Open-Label Extension Phase

Eligible participants will have the option to enter the OLE phase of the study. Refer to the OLE SoA (Section 1.3.2) for study visits and timing of assessments, and Section 4.1.2 and Table 7 for overall design and additional details of the OLE phase.

6.7.2. Inclusion Criteria - Open-Label Extension Phase

Participants are eligible to be included in the OLE phase only if all the following criteria apply:

1. Participant is enrolled in the double-blind phase when all the required number of PFS events have been observed and the primary PFS analysis has been completed;

   OR

   Participant is randomized to receive placebo in the double-blind phase and experiences disease progression (confirmed by central review using RECIST v1.1);

   OR

   Participant is randomized to receive nirogacestat in the double-blind phase and experiences disease progression (confirmed by central review using RECIST v1.1) but is deriving clinical benefit without significant toxicity as determined by the investigator and confirmed by the medical monitor. Refer to Section 11.1.3 for the medical monitor contact details.

2. Participant has adequate organ and bone marrow function as outlined in the double-blind inclusion criteria 8 (based off of hematology and serum chemistry results within 14 days prior to enrollment in the OLE phase).
3. Participant agrees to use contraception as outlined in the double-blind inclusion criteria 10.
4. Participate is capable of giving signed informed consent specific to the OLE phase, as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

6.7.3. Exclusion Criteria - Open-Label Extension Phase

Participants are excluded from the OLE phase of the study if any of the following criteria apply:

1. Participant requires surgery to prevent organ dysfunction.
2. Participant has prematurely discontinued from the double-blind phase for any reason other than disease progression (confirmed by central review using RECIST v1.1).
3. Participant developed a concurrent illness/condition that, in the opinion of the investigator, would represent a risk to overall health if they enroll in this study.

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

It may be necessary for a participant to permanently discontinue study treatment early. If study treatment is permanently discontinued early, the participant will not remain in the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study treatment during the EOT visit. Participants will be required to return to the site for a follow-up visit 30 to 45 days after the last dose of study treatment.

Reasons for discontinuation of study treatment early may include:

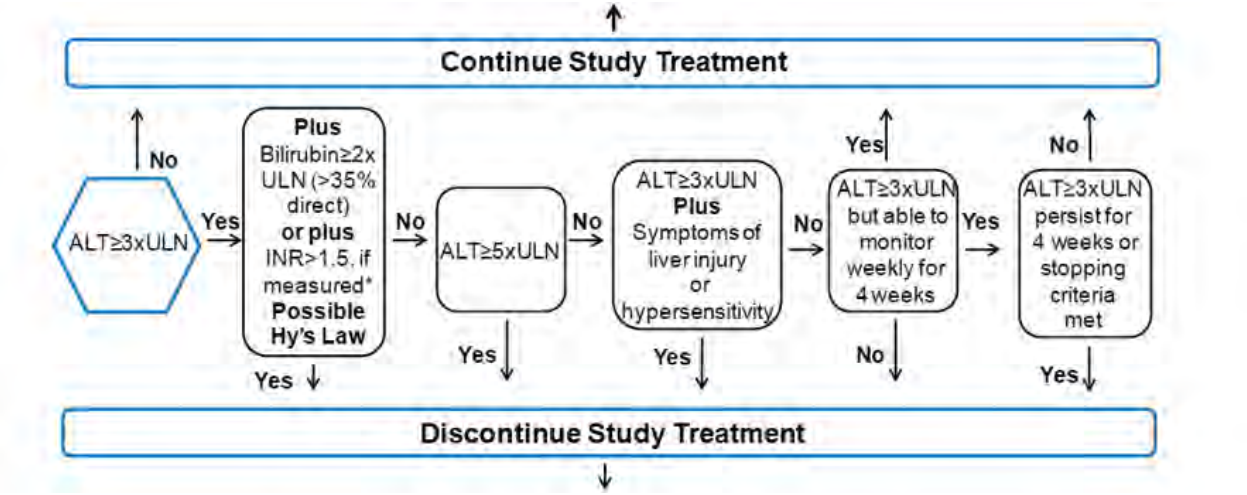
- Participants in the double-blind phase who meet the definition of disease progression (confirmed by central review using RECIST v1.1) and do **not** enter the OLE phase;
- Participants in the OLE phase who meet the definition of disease progression (confirmed by central review using RECIST v1.1);
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the requirements of the protocol;
- Any SAE (refer to Section 10.3.2 for SAE criteria), clinically significant AE (refer to QTc stopping criteria, Section 7.1.2), severe laboratory abnormality (refer to liver chemistry stopping criteria, Section 7.1.1), intercurrent illness, or other medical condition which indicates to the investigator that continued participation is not in the best interest of the participant;
- Pregnancy (refer to Sections 8.3.5 and 10.4 for additional details);
- Requirement of prohibited concomitant medication (refer to Section 6.5.1.1 for known drug interactions);
- Participant failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the sponsor or the regulatory authority.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Figure 1 or if the investigator believes that it is in the best interest of the participant.

Figure 1 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm

- **If participant is to be monitored weekly, must refer to Liver Safety: Suggested Actions and Follow-up Assessments (Section 10.6)**



- **Must refer to Liver Safety: Suggested Actions and Follow-up Assessments (Section 10.6)**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN and Bilirubin ≥2xULN (>35% direct) or INR>1.5, if measured*

*INR value not applicable to participants on anticoagulants

Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECGs printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc >500 msec
- Change from baseline of QTc >60 msec

Table 5 describes the discontinuation criteria for participants with underlying bundle branch block.

Table 5 Bundle Branch Block Discontinuation Criteria

Baseline QTc with Bundle Branch Block	Discontinuation QTc Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

See the SoA for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.3. Pregnancy

A female participant who becomes pregnant will be withdrawn from study treatment. See Section 10.4 and Section 8.3.5 for additional details.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, the EOT visit should be conducted. See SoA (Section 1.3) for specific data to be collected at the time of study discontinuation, as well as follow-up for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and,

if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria (Sections 5.1, 5.2, 6.7.2, and 6.7.3). The electronic data capture (EDC) will capture all participants who sign the ICF, including all screen-failures.
- The maximum amount of blood collected from each participant will not exceed 133 mL each year throughout the double-blind and OLE phases of the study, including any extra assessments that may be required. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Refer to Table 6 and Table 7 for a summary of the study phases and the associated study visits. Refer to the SoA for a complete list of study assessments and their timing associated with each study visit, and the study reference manual for study visit checklists with recommended sequence of assessments.

Table 6 Double-Blind Phase Study Visits

Double-Blind Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA (Section 1.3.1) for the complete list of study assessments and the timing associated with each study visit for the double-blind phase)
Screening	Up to 28 days prior to first dose.	• On day 1 of the screening period, participants will be trained on a home ePRO device, and will complete the screening PROs over the next 7 days (Section 8.1.2). • CT or MRI (Section 8.1.1.1) scans acquired prior to the participant signing ICF may be used as screening time point scans if they were obtained within 28 days of the first dose of study treatment and the participant meets study requirements. • Fresh tumor biopsy to be done prior to MRI scan, if available.

Double-Blind Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA (Section 1.3.1) for the complete list of study assessments and the timing associated with each study visit for the double-blind phase)
Baseline (Cycle 1 Day 1 = first dose of study treatment)	Up to 48 hours prior to first dose (first dose may not occur until ≥day 21 of the screening period to allow for at least 1 week between screening and baseline PROs).	• The following baseline assessments are to be conducted prior to the first dose of study treatment: o PROs using home ePRO device (7 days prior to first dose); o Physical examination; o Vital signs; o Weight; o Pre-dose 12-Lead ECGs (should be done after vital signs and prior to blood draws); o ECOG performance status; o Urinalysis; o Urine pregnancy for woman of childbearing potential (WOCBP); o Blood draws for clinical laboratory parameters and optional pharmacogenomic sample; o MRI for tumor volume (if not conducted at screening); o Concomitant medication and AE/SAE review; and o Pre-dose PK blood draw. • After the pre-dose baseline assessments (noted above) have been completed, participants will be randomized to study treatment (placebo or nirogacestat) in a 1:1 ratio and will take first dose of study treatment (150 mg) at the site. • The following baseline assessments are to be conducted following the first dose of study treatment: o Triplicate 12-Lead ECGs (Section 8.2.3) to be conducted 1-hour post-dose; o PK sampling (Section 8.5) to be conducted at 0.25, 0.5, 1, 1.5 and 2 hours post-dose; and o 2-hour observation period following the first dose of study treatment.

Double-Blind Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA (Section 1.3.1) for the complete list of study assessments and the timing associated with each study visit for the double-blind phase)
Cycle 1 Day 8	Week 2 / day 8 (±2 days)	• Participants will be instructed to **not** take their planned morning dose of study treatment at home on the day of this visit. Instead the morning dose will be taken at the site following the pre-dose PK blood draw. • Triplicate 12-Lead ECGs will be required 1-hour post-dose with a ±10 minute allowed window.
Cycle 1 Day 15	Week 3 / day 15 (±2 days)	• Refer to SoA
Cycle 1 Day 22	Week 4 / day 22 (±2 days)	• Refer to SoA
Cycle 2 Day 1	Week 5 / day 29 (±2 days)	• Refer to SoA
Cycle 4 Day 1	Week 13 / day 85 (±7 days)	• Refer to SoA
Cycle 7 Day 1 and Every 3 Cycles	Week 25 / day 169 and On (±7 days)	• Following the Cycle 7 Day 1 visit, participants will return to the site every 3 cycles until EOT. • If MRI to assess tumor volume and CT to assess RECIST v1.1 are conducted on the same day, MRI with no contrast must be performed prior to CT with contrast.
End of Treatment (EOT) visit	Disease progression: Participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments but should be within 14 days of disease progression confirmation. Other reason for EOT: Participant will be encouraged to return to the site as soon as possible to complete	• Applicable if: o Participant experiences disease progression (confirmed by central review using RECIST v1.1); o Participant discontinues study treatment for any other reason; o Study is stopped by the sponsor for any reason; or o All required number of PFS events have been observed and the primary PFS analysis has been completed. • Should be conducted prior to study treatment discontinuation or as close as possible to last dose of study treatment. • May be conducted over a 2-day period.

Double-Blind Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA (Section 1.3.1) for the complete list of study assessments and the timing associated with each study visit for the double-blind phase)
	the EOT visit assessments but should be done within 28 days of notification.	• Will serve as the OLE baseline visit if the participant is eligible and chooses to enroll in the OLE phase. • MRI or CT scans at this visit are only required if not performed within the past 3 months.
Follow-up visit	Participant will return to the site for the follow-up visit 30 days (+7 days) after the last dose of study treatment.	• Applicable only if participant is not continuing in the optional OLE phase.
Monthly wellness checks	Monthly	• Telephone or email contact is required throughout the study. • Refer to Section 8.2.7.
Monthly urine pregnancy tests	Monthly	• WOCBP (only) will take monthly pregnancy tests provided by the sponsor at home or during a scheduled study visit. • Home pregnancy test results will be recorded in the home ePRO device by the participant. • Refer to Section 8.2.6.
Unscheduled visits	Anytime during the study	• Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Open-Label Phase Study Visits

OLE Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA Section 1.3.2 for the complete list of study assessments and the timing associated with each study visit for the OLE phase)
Baseline (Cycle 1 Day 1 = first dose of OLE study treatment)	Same visit as the double-blind EOT visit.	• OLE phase is for eligible participants (refer to Sections 6.7.2 and 6.7.3 for OLE specific eligibility criteria) to receive open-label study treatment (nirogacestat). • The double-blind EOT visit will serve as the OLE baseline visit. All double-blind EOT visit assessments, as described in the double-blind SoA (Section 1.3.1), will be conducted prior to

OLE Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA Section 1.3.2 for the complete list of study assessments and the timing associated with each study visit for the OLE phase)
		unblinding the participant's study treatment and prior to the first dose of open-label study treatment. • At baseline, blood draws for clinical chemistry will be done as part of the double-blind EOT visit (prior to unblinding). However, if clinical chemistry labs have not been conducted within the past 14 days prior to baseline, an additional blood draw will be required for same day local laboratory processing to reconfirm adequate organ and bone marrow function (refer to double-blind inclusion criteria 8) and must be done prior to first dose of open-label study treatment. • The following assessments are required at the OLE baseline visit: o Participant to complete all double-blind phase EOT visit assessments and investigator or qualified designee to assess all ongoing AEs/SAEs for causality in a blinded manner; o Participant to sign ICF (specific to the OLE phase); o Confirm participant meets all I/E criteria specific to the OLE phase (refer to Sections 6.7.2 and 6.7.3); o Draw blood for clinical chemistry assessment for local lab processing (only if labs not done within the past 14 days); o Enroll participant in the OLE phase using the IRT and disease study treatment; o Conduct pre-dose PK blood draw (only applicable for participants who were previously randomized to placebo in the double-blind phase); o Conduct triplicate 12-Lead ECGs 1-hour post-dose (only applicable for participants who were previously randomized to placebo in the double-blind phase);

OLE Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA Section 1.3.2 for the complete list of study assessments and the timing associated with each study visit for the OLE phase)
		○ Conduct PK sampling at 0.25, 0.5, 1, 1.5 and 2 hours post-dose (only applicable for participants who were previously randomized to placebo in the double-blind phase); and ○ Complete the 2-hour observation period following the first dose of study treatment (only applicable for participants who were previously randomized to placebo in the double-blind phase).
Cycle 1 Day 8	Week 2 / day 8 (±2 days)	• Applicable only to participants who were previously randomized to receive placebo in the double-blind phase. • Participants will be instructed to **not** take their planned morning dose of study treatment at home on the day of this visit. Instead the morning dose will be taken at the site following the pre-dose PK blood draw. • Triplicate 12-Lead ECGs will be required 1-hour post-dose with a ±10 minute allowed window.
Cycle 1 Day 15	Week 3 / day 15 (±2 days)	• Applicable only to participants who were previously randomized to receive placebo in the double-blind phase.
Cycle 1 Day 22	Week 4 / day 22 (±2 days)	• Applicable only to participants who were previously randomized to receive placebo in the double-blind phase.
Cycle 2 Day 1	Week 5 / day 29 (±2 days)	• Applicable only to participants who were previously randomized to receive placebo in the double-blind phase.
Cycle 4 Day 1	Week 13 / day 85 (±7 days)	• Applicable to all participants.
Cycle 7 Day 1	Week 25 / day 169 (±7 days)	• Applicable to all participants.
Cycle 10 Day 1	Week 37 / day 253 (±7 days)	• Applicable to all participants.

OLE Phase Visit Name	**Week/Calendar Day (visit window)**	**Comments** (refer to the SoA Section 1.3.2 for the complete list of study assessments and the timing associated with each study visit for the OLE phase)
Cycle 13 Day 1 and Every 3 Cycles	Week 49 / day 337 and On (±7 days)	• Applicable to all participants. • Following the Cycle 13 Day 1 visit, participants will return to the site every 3 cycles until EOT.
End of Treatment (EOT) visit	Disease progression: Participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments but should be within 14 days of disease progression confirmation. Other reason for EOT: Participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments but should be done within 28 days of notification.	• Applicable if: o Participant experiences disease progression (confirmed by central review using RECIST v1.1); o Participant discontinues study treatment for any other reason; o Study is stopped by the sponsor for any reason; or o Nirogacestat becomes commercially available. • Should be conducted prior to study treatment discontinuation or as close as possible to last dose of study treatment. • May be conducted over a 2-day period. • MRI or CT scans at this visit are only required if not performed within the past 3 months.
Follow-up visit	Participant will return to the site for the follow-up visit 30 days (+7 days) after last dose of study treatment.	• Applicable only if participant is not transitioning directly to commercial nirogacestat at the time of discontinuation.
Monthly wellness checks	Monthly	• Refer to Table 6.
Monthly urine pregnancy tests	Monthly	• Refer to Table 6.
Unscheduled visits	Anytime during the study	• Refer to Table 6.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1. Tumor Imaging

Sites will submit all CT and MRI scans for independent, blinded centralized radiologic review throughout the double-blind and OLE study phases. Before the study is initiated at each site, sites will be trained on imaging requirements and guidance on how to submit scans. Refer to the imaging acquisition manual and the imaging submission manual, which describe the imaging methods and submission process that sites must follow.

8.1.1.1. Tumor Assessment Using RECIST Version 1.1 Criteria

Tumor assessment for primary and secondary endpoints (PFS and ORR, respectively) will be measured by CT (contrast required unless contraindicated) or MRI (no contrast required) using RECIST v1.1 (Eisenhauer, 2009) at screening and during the double-blind and OLE phases as specified in the SoA, and whenever disease progression is suspected (e.g., symptomatic deterioration). The imaging modality will be determined by the investigator and the same imaging modality used to measure the identified and reported lesion at screening in the double-blind phase must be used at each subsequent visit throughout the double-blind and OLE phases.

During the 28-day screening period, participants will be evaluated by imaging (CT or MRI) to confirm that they have DT/AF that has progressed by ≥20% as measured by RECIST v1.1 within the 12-month period prior to first dose of study treatment (double-blind inclusion criteria 2). The screening scans will be submitted and reviewed centrally; however, participant enrollment will not dependent on central review.

Scans acquired prior to the participant signing ICF may be used as screening time point scans if they were obtained within 28 days of the first study treatment administration and the participant meets study requirements. These scans will then be collected, stored, and documented as the screening scan. No other pre-enrollment images will be collected or stored for the study.

8.1.1.2. Volumetric Assessment

The MRI imaging for tumor volumetrics is a required assessment in the double-blind phase only (not required in the OLE phase), as described in the SoA.

If MRI is used to assess RECIST v1.1 at screening, then MRI will not be repeated at the baseline visit. Both CT and MRI assessments may be conducted on the same day, but MRI with no contrast must be performed prior to CT with contrast.

8.1.2. Patient-Reported Outcomes

The PRO questionnaires will be completed by each participant as described in the SoA using a home ePRO device. The participant will receive their ePRO device at the screening visit and will be expected to return the device at the end of study participation.

The PRO assessments should be completed before any other assessments or study procedures and before discussion of disease progression to avoid bias in the participant's responses to the questions.

Participants will complete the PRO questionnaires using their home ePRO devices monthly throughout the double-blind phase. In the OLE phase, the PROs will be administered monthly throughout the first year and then every 3 months thereafter. The PROs will always be administered the week prior to a study visit when applicable and in this order: 1) BPI short form, 2) MDASI), 3) desmoid-specific symptoms PRO assessment, 4) desmoid-specific impacts PRO assessment, 5) PGIS, and 6) PGIC.

The BPI short form, MDASI and desmoid-specific symptoms PRO assessment will be administered for 7 consecutive days once a month with a 24-hour recall period throughout the study.

The desmoid-specific impacts PRO assessment, PGIS and PGIC will be administered on the last day of the 7-day PRO assessments noted above, with a 7-day recall period. The PGIC is omitted at the screening and baseline visits.

On day 1 of the screening visit, the participate will receive training on how to use the home ePRO device, which will include a practice questionnaire to be completed prior to the participant leaving the site. The participant will complete the screening visit PROs over the next 7 days. The baseline visit PROs should be should be administered 7 days prior to the baseline visit with at least 1 week between the screening and baseline PRO assessments.

Refer to the study reference manual for more information on the PROs and user guides for administration.

8.1.2.1. Patient Global Impression of Severity

The PGIS is a single item scale that evaluates the participant's perception of the overall severity of their desmoid related symptoms over the past week on a 4-point scale ranging from "none" to "severe."

8.1.2.2. Patient Global Impression of Change

The PGIC is a single item scale that evaluates the participant's perception of the overall change in their overall status since the start of the study treatment on a scale ranging from "very much better" to "very much worse."

8.1.2.3. Brief Pain Inventory Short Form

The BPI is a measurement tool for assessing clinical pain and allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. The short form version of the BPI consists of 9 questions and will utilize an 11- point numeric rating scale (NRS) from 0-11 with a 24-hour recall period.

8.1.2.4. MD Anderson Symptom Inventory

The MDASI is a multi-symptom PRO measure for clinical and research use. The MDASI's 13 core items include symptoms found to have the highest frequency and/or severity in patients with various cancers and treatment types. The MDASI utilizes an 11-point NRS from 0-10 to measure severity, from "none" to "as bad as you can imagine," with a 24-hour recall period.

8.1.2.5. Desmoid-Specific PRO

The desmoid-specific PRO tool was developed by Memorial Sloan Kettering Cancer Center/Desmoid Tumor Research Foundation and IQVIA to measure signs and symptoms of desmoid tumors and their impact on patients' lives. The tool consists of items assessing the severity of key signs and symptoms (11 items), including pain, fatigue, swelling, muscle weakness, difficulty moving, and tumor location-specific signs/symptoms; the impact of these symptoms on functioning and daily living (17-items).

The signs and symptoms items are evaluated on an 11-point NRS from 0-10 to measure severity from "none" to "as bad as you can imagine," with a 24-hour recall period. The impact items are evaluated either on an 11-point NRS to measure severity, or a 5-point Likert Scale ranging from "none of the time" to "all of the time" to measure frequency, with a 7-day recall period.

8.1.3. Tumor Biopsy

Core needle biopsies (archival tissue may be used, if available) will be collected from all participants prior to receiving study treatment during the screening period (when applicable, fresh tumor biopsies must be taken after MRI if assessments occur at the same visit). Tumor samples will be used to confirm desmoid diagnosis for all participants. However, participant enrollment will not be dependent on central review. Additionally, archival or fresh tumor biopsies collected at screening will be used for somatic genotyping (unless prohibited by local regulations) (Section 8.7).

For participants consenting to the optional pharmacogenomics research, an additional tumor biopsy will be collected at the EOT visit.

Ideally, 2 cores will be collected before and after initiation of study treatment and will be used for the correlative studies (i.e., 2 cores at screening and 2 cores at the EOT visit).

Tumor specimens will be stored as formalin-fixed, paraffin embedded (FFPE) blocks at room temperature. If the FFPE block cannot be made available, 15 unstained slides will be used in

place of 2 cores. Instructions for handling, processing and shipment of tumor biopsies will be provided in the central laboratory manual.

Refer to Section 8.8 for details on biomarkers.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Demographics Data and Medical History

Demographic data will include age or date of birth, sex, and self-reported race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (i.e., WOCBP or no WOCBP); history of alcohol consumption (i.e., presence or absence); and review of concomitant medications.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator.

8.2.2. Physical Examinations and Eastern Cooperative Oncology Group Performance status

Complete or brief physical examinations, as well as height/weight, and assessment of ECOG performance status (Section 10.8) will be required throughout the study as described in the SoA. Height to be measured at screening only.

A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, heart and abdomen.

Investigators should pay special attention to clinical signs related to previous serious illnesses, and changes from baseline will be recorded in the source documentation. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF page.

Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

8.2.3. Electrocardiograms

Triplicate 12-Lead ECGs readings (done 2-3 minutes apart and averaged) will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals, at the timepoints described in the SoA. Prior to the ECG assessments, participants should rest in a semi-recumbent supine position for at least 5 minutes.

The ECGs should be performed after vital signs are collected and prior to blood draws, when applicable.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the source documentation at the site.

Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.4. Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed throughout the study as described in the SoA.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.5. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments as defined in Section 10.2, must be conducted in accordance with the central laboratory manual and the SoA.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study on the AE page of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with abnormal values considered to be clinically significant during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.6. Pregnancy Testing

Pregnancy testing will only be required for women of childbearing potential (WOCBP) (refer to Section 10.4 for definition of WOCBP and additional details on contraceptive guidelines and collection of pregnancy information).

A negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (prior to first dose of double-blind study treatment) will be required to meet study entry criteria.

Monthly urine pregnancy tests will be required for WOCBP throughout the duration of the double-blind and OLE phases. In between study visits, participants will administer home urine dipstick pregnancy tests provided by the sponsor and the participants will record the results in their home ePRO device.

8.2.7. Monthly Wellness Checks

Monthly telephone or email contact is required throughout the double-blind and OLE phases of the study and may be replaced by a face-to-face interaction when study visits occur if the information can be obtained during the visit.

A copy of the telephone report or email must be documented in the source documentation. Email must not replace direct follow-up by phone or in clinic for clinically significant AEs or other emergent issues. Adverse events and concomitant medications changes will be captured in the associated eCRFs.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Sections 10.3.1 and 10.3.2, respectively.

An AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the time of signing ICF until 30 days after the last dose of study treatment at the time points specified in the SoA (Section 1.3) throughout the double-blind and OLE study phases.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the medical history/current medical conditions section of the eCRF (not the AE section).

All SAEs will be recorded and reported to the sponsor's safety vendor, United BioSource LLC (UBC), immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.4. The investigator will submit any updated SAE data to UBC within 24 hours of it being available.

To report the SAE, the SAE form will be completed electronically in the EDC system. When the form is completed, UBC will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, a paper SAE form should be completed, scanned and emailed to UBC at [redacted]. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Investigators are not obligated to actively seek AEs and/or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and/or SAEs, and the procedures for completing and transmitting SAE reports are provided in Section 10.3.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Within 24 hours of receipt of follow-up information, the investigator must update the SAE form in the EDC system for the study and submit any supporting documentation if requested to UBC. Further information on follow-up procedures is given in Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 30 days after the last dose of study treatment.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For this study, any dose of study treatment greater than 300 mg daily dose of study treatment within a 24-hour period will be considered an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately (refer to Section 11.1.3 for contact information).
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 4 days.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

- Sparse PK samples will be collected during the study, as described in the SoA (Section 1.3) to inform development of a population PK model of nirogacestat.
- Whole blood samples of approximately 3 mL each will be collected for measurement of serum concentrations of nirogacestat as specified in the SoA.
- Blood samples for PK analysis will be collected in the double-blind phase for all participants. Only participants who were previously randomized to placebo in the

double-blind phase will be required to have blood samples collected for PK analysis in the OLE phase.

- Refer to the SoA (Section 1.3) for details on PK sampling time points.
- All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and eCRF.
- The actual date and time (24-hour clock time) of each sample will be recorded.
- Instructions for the collection, handling, and shipment of pharmacokinetic samples will be in the central laboratory manual.
- Samples will be used to evaluate the PK of nirogacestat.
- Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.
- Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6. Pharmacodynamics

Optional blood and tumor samples will be collected for the evaluation of pharmacodynamic biomarkers (refer to Section 8.8).

8.7. Genetics

- A blood sample and tumor biopsy (archival sample may be used) will be collected from all participants (unless prohibited by local regulations) prior to the first dose of study treatment to perform genotyping for germline and somatic mutation in APC and CTNNB1 genes to determine the frequency of these mutations in desmoid tumors. Response to study treatment based on mutational status may be evaluated.
- In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.
- Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual.

- Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last study visit at a facility selected by the sponsor to enable further analysis of biomarker responses to nirogacestat.
- Refer to Section 10.5 for information regarding genetic research.

8.8. Biomarkers

- Participation is optional for genetic research and those who do not wish to participate may still enroll in the study.
- The following optional tumor and blood samples for biomarker research will be collected from consenting participants only, as specified in the SoA (Section 1.3):
    - Before study treatment initiation samples:
        1. Pharmacogenomic blood sample
        2. Archival or fresh tumor tissue sample
    - After study treatment initiation sample:
        3. Fresh tumor tissue sample
- Analyses may include the following: (1) expression analysis of genes and proteins associated with the Notch pathway, (2) molecular analysis of genomic alterations associated with Notch signaling (for example, Notch 1 mutations), (3) levels of NICD, (4) molecular profiling of tumor cells to identify potential markers of response/resistance to nirogacestat.
- Additional biomarkers may also be measured, based on emerging clinical and literature data pertaining to Notch biology. Full details regarding collection, processing, storage and shipping of all PD biomarker samples will be provided in the central laboratory manual.
- Samples will be tested for expression on Notch pathway genes to evaluate their association with the observed clinical responses (e.g., PFS or ORR) to study treatment.
- Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last study visit at a facility selected by the sponsor to enable further analysis of biomarker responses to nirogacestat.

8.8.1. RNA Transcriptome Research

Transcriptome studies may be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood and tumor sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to desmoid tumors or the action of nirogacestat.

The same samples may also be used to confirm findings by application of alternative technologies.

8.8.2. RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative reverse transcriptase polymerase chain reaction, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in an RNA expression profile for each blood and tumor sample. The RNAs assayed may be those involved with the pathogenesis of desmoid; the absorption, distribution, metabolism, or excretion of nirogacestat; or in the participant's response to nirogacestat. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to nirogacestat or the pathogenesis of desmoid. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to desmoid or the action of nirogacestat.

8.8.3. Proteome Research

Plasma and tumor proteome studies may be performed by 2-D gel separation, and/or peptide mass mapping, or an alternative equivalent procedure. Proprietary algorithms and standard statistical techniques, such as analysis of variance and analysis of covariance, may be used to identify individual proteins exhibiting statistically significantly different changes in their levels between samples and/or between groups of samples. These differentially expressed proteins will be identified by mass spectrometry or equivalent technology. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to desmoid and medically related conditions or the action of nirogacestat.

The samples may also be used to confirm findings by application of alternative technologies.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

Nirogacestat treatment will increase the time to progression compared to placebo in participants with desmoid tumors. The null hypothesis will be rejected if the HR is >0.4.

The following hypothesis will be tested using a stratified log-rank test:

H0: PFS(t)placebo = PFS(t)nirogacestat

Ha: PFS(t)placebo < PFS(t) nirogacestat

where PFS(t) represents the progression free survivorship function at time, t

9.2. Sample Size Determination

The study sample size is based on the PFS endpoint. A total of 51 events will provide 90% power and a 1-sided type 1 error rate of 0.025 (1-side hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat group is 20 months and 8 months in the placebo group (corresponding to a hazard ratio of 0.4 relative to placebo). Assuming a 10% dropout rate, 94 participants will be randomized in a 1:1 ratio to observe the required number of events.

The assumptions selected for sample size estimate are based partially on the results reported in Gounder, 2018. As outlined in Section 2.2.3, a randomized double-blind Phase 3 study was conducted in desmoid participants comparing sorafenib to placebo. The study established a median PFS of 9.6 months for the placebo participants; but the population enrolled was a more heterogeneous desmoid population with only approximately 43% of the placebo participants having progressing tumors. The NIR-DT-301 study will only enroll progressing participants; therefore, a shorter median of 8 months PFS for placebo was used to calculate the sample size.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Intent-to-Treat (ITT)	The Intent-to-Treat (ITT) Population will consist of all participants who are enrolled and randomized to study treatment. Participants will be analyzed according to the treatment they were randomized to and the strata to which they have been assigned. Participants who were randomized but did not

Population	Description
	subsequently go on to receive study treatment are included in the ITT population.
Per-Protocol Population	The Per-Protocol Population will be defined for supportive analysis and will consist of those participants who have no major protocol deviations, including mis-randomizations or mis-stratifications. Participants will be analyzed according to the study treatment actually received (i.e., at least 1 dose of the study treatment).
Safety	The Safety Population will consist of all participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Detailed methodology for summary and statistical analyses of the data collected in this study will be documented. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary efficacy endpoint is PFS, which is defined as the time from randomization until the date of assessment of progression or death by any cause. Progression will be assessed by independent, blinded central review using RECIST v1.1 (Eisenhauer, 2009). The primary efficacy endpoint, PFS, will be analyzed using a 1-sided stratified log-rank test to compare the distributions between nirogacestat and placebo at a 1-sided alpha level of 0.025. The primary analysis of PFS will be performed on the ITT Population, defined as all participants who are randomized to study treatment after the required number of PFS events have been observed. Participants in the ITT Population will be analyzed in the study treatment arm to which they are randomized.

	Progression-free survival data will be summarized with Kaplan-Meier methodology. Two-sided 95% CIs for the median time-to-event in each study treatment arm, the event rates at specific time points, and the hazard rate ratio will be computed. There will be a central review manual provided to the central reader and an imaging review charter provided to the sponsor that will clearly detail the entire process.
Secondary	Secondary endpoints include: • Overall response rate, defined as the proportion of participants with CR + PR assessed by RECIST v1.1; • Change in tumor volume from baseline as assessed by MRI volumetric; • Change in PRO measures (BPI short form, MDASI, and desmoid-specific PRO assessment) from baseline; and • Duration of response for participants whose best response is CR or PR. In order to preserve the total type I error for the study, secondary endpoints will be evaluated in a hierarchical fashion according to the order that will be outlined in the SAP. Testing will only be performed if the null hypothesis of the primary endpoint is rejected. Overall response rate will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. Change in tumor volume assessed by MRI will be analyzed using a repeated measures model adjusting for baseline tumor volume and randomization strata. The Wilcoxon test will be used to compare the change from baseline to the last assessment in total scores for MDASI. In addition, a mixed model repeated measures analysis will be conducted. Summary statistics on the actual scores and changes from baseline in total score and sub-scores for symptoms will be reported and displayed graphically. In addition, descriptive statistics will be used to summarize duration of response, pain inventory, and desmoid-specific PRO. A repeated measured analysis model will be used to compare the BPI scores over time between treatment groups. All data collected after crossover to nirogacestat (for participants who were previously randomized to placebo in the double-blind phase and receive nirogacestat in the OLE phase after disease progression) will be analyzed and reported separately.

Exploratory	Will be described in the SAP finalized before database lock.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Safety Endpoints	The safety and tolerability of nirogacestat will be evaluated by means of study treatment-related AE reports, physical examinations, and laboratory safety evaluations. Adverse events will be graded by the investigator according to the CTCAE v5.0 and coded using the Medical Dictionary for Regulatory Activities. The focus of AE summaries will be on Treatment Emergent AEs, those with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. Clinical laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and study visit. Descriptive statistics for the actual values (and/or change from baseline) or frequencies of clinical laboratory parameters over time. Incidence of abnormalities and shift tables will be presented.

9.4.3. Other Analyses

Pharmacokinetic, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

9.5. Interim Analyses

One interim analysis may be performed after 26 PFS events (corresponding to approximately 50% of the total events) have been observed. Progression will be determined by independent, blinded central review determination for this analysis. A Lan-DeMets alpha-spending function with an O'Brien-Fleming stopping boundary will be used for the interim analysis of PFS. The study may be stopped for overwhelming efficacy or futility.

At the interim analysis, the study may be stopped for futility if the observed hazard ratio is greater than 0.91 or stopped for overwhelming efficacy if the hazard ratio is less than or equal to 0.31 in favor of nirogacestat. This is equivalent to a Z-score greater than -0.252 for futility or less

than -2.96 for efficacy. The alpha spent for the interim testing is 0.002 and the remaining 0.023 alpha will be allocated to the final analysis.

The analysis will be conducted by an independent committee consisting of at least 1 statistician. Results of the interim analysis will not be disseminated among investigators or anyone directly involved in study conduct.

The interim analysis plan will describe the planned interim analyses in greater detail.

9.5.1. Data Monitoring Committee

The study will utilize an independent data monitoring committee (DMC) and will operate according to an established charter. The committee will be composed of approximately 3 to 4 members including physicians knowledgeable in the treatment of desmoid tumors and an independent statistician. Sponsor employees will not be members of the DMC. The DMC will be responsible for ongoing monitoring of the blinded safety, efficacy and benefit/risk profile of participants in the study. Reviews will include aggregate safety, targeted medical events of special interest, serious AE data and aggregate endpoint data.

Following each data review, the DMC may recommend 1) no changes to the study are needed, 2) changes to the protocol or informed consent based on clinical safety findings, or 3) early termination of the study based on safety analyses. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the sponsor for final decision. Additionally, the DMC may be asked to assist the sponsor in evaluating the impact of data from other company-sponsored studies or other published studies.

The DMC charter will outline the frequency of meetings and detail all aspects of DMC's scope of review and procedures.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines; and
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board/independent ethics committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of serious adverse event or other significant safety findings as required by IRB/IEC procedures; and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A separate consent is required for collection of pharmacogenomic samples (blood and tumor biopsies).
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.6. Dissemination of Clinical Study Data

10.1.7. Data Quality Assurance

- All participant data relating to the study will be entered into the electronic case report forms (eCRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be indicated in the monitoring plan to ensure the protocol and GCP is followed.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator according to specifications in the ICH guidelines, local regulations, or as specified in the clinical trial agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Investigators will maintain records separate from the eCRFs in the form of clinical charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the participant signed informed consent prior to participation in the study. Source documents must completely reflect the nature and extent of the participant's medical care and must be available for source document verification against entries in the eCRFs when the sponsor's monitor visits the site. In order to meet data integrity requirements, source documentation should be attributable, legible, contemporaneous, accurate, available/accessible, original, complete and credible. All information obtained from these documents will be kept in strict confidentiality. Definition of what constitutes source data can be found in the study reference manual.

10.1.9. Study and Site Closure

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Study-site closure prior to completion of the study should be avoided. The investigator and sponsor will agree to the circumstances that could cause early study-site closure.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator; or
- Discontinuation of further study treatment development.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the electronic case report form.
- Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5 and Section 6.7.1 of the protocol.
- Additional tests, as part of unscheduled visits, may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing (urine or serum as described in the SoA; Section 1.3) will be conducted at monthly intervals during the double-blind and OLE study treatment phases.
- Pregnancy testing (urine or serum as described in the SoA) will be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in the Inclusion Criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.
- Pregnancy testing details are detailed in Section 5.1.
- Investigators must document their review of each laboratory safety report.

Table 8 Protocol-Required Safety Laboratory Assessments

Hematology	**Chemistry**[2]	**Urinalysis**	**Serology**[5]

• HGB
• HCT
• PLT count
• RBC count
• RBC Indices:
  o MCV
  o MCH
• %Reticulocytes
• WBCC with Differential[1]:
  o neutrophils
  o lymphocytes
  o monocytes
  o eosinophils
  o basophils
	• AST/SGOT
	• ALT/SGPT
	• D-BIL
	• TBIL
	• GGT
	• Sodium
	• Chloride
	• Potassium
	• Bicarbonate
	• Inorganic phosphorus
	• Alkaline phosphatase
	• Creatinine[3]
	• Estimated glomerular filtration rate
	• BUN
	• Glucose (non-fasting)
	• Uric acid
	• Albumin
	• Total protein
		• Specific gravity
		• Bilirubin
		• Glucose
		• Leukocyte esterase
		• Nitrite
		• Protein
		• Urobilinogen
		• Blood
		• Ketones
		• pH
		• Microscopy[4]
			• HIV antibody
			• HBV
			  o HBsAg
			• HCV
			  o hepatitis C antibody (HCV PCR if hepatitis C antibody positive)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; D-BIL = direct bilirubin; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCT = hematocrit; HCV = hepatitis C virus; HGB = hemoglobin; HIV = human immunodeficiency virus; MCH = mean cell hemoglobin; MCV = mean cell volume; PCR = polymerase chain reaction; PLT = platelet; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT =serum glutamic-pyruvic transaminase; TBIL = total bilirubin; WBCC = white blood cell count

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.
2. Details of liver stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Sections 7.1.1 and 10.6.
3. If creatinine >1.5 × ULN then calculated creatinine clearance should be ≥60 mL/min/1.73m^2 (using the Cockcroft-Gault formula).
4. Microscopy examination is performed only if blood or protein is abnormal.
5. Serology only required at screening.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Event (AE)

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE or serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. 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 AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent disability/incapacity**

- 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include 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.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the electronic case report form (eCRF).
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to United BioSource, LLC (UBC) in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UBC. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UBC.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of all SAEs/AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For those SAEs/AEs not listed in the CTCAE, the following grading system should be used:

- CTCAE **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- CTCAE **Grade 2** Moderate; minimal, local or noninvasive treatment indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- CTCAE **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- CTCAE **Grade 4** Life-threatening consequences; urgent treatment indicated.
- CTCAE **Grade 5** Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (Section 10.3.2), **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure, when making an assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to UBC. However, **it is very**

important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UBC.

- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UBC to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide UBC with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the UBC within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to UBC via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to UBC will be using the electronic data capture (EDC) system.
- If the EDC system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the EDC system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC system has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UBC safety department by telephone or email.
- Contacts for SAE reporting can be found in Section 11.1.4.

SAE Reporting to UBC via Paper CRF
• Email transmission of the SAE paper CRF is the preferred method to transmit this information to UBC. If email is unavailable, the SAE form can be faxed to UBC. • In rare circumstances and in the absence of email or facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE eCRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Section 11.1.4.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP) is defined as a woman that is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy; or
   - Documented bilateral salpingectomy; or
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o Oral o Intravaginal o Transdermal o Injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Two forms of highly effective birth control must be used throughout the study and during follow-up as specified for each gender (Section 5.1). Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information:

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

10.5. Appendix 5: Genetics

Use and analysis of deoxyribonucleic acid (DNA):

- Genetic variation may impact a participant's response to study treatment, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and institutional research boards/independent ethic committees allow, DNA analysis will be collected from participant's blood sample (referred to as the optional pharmacogenetic blood sample in the SoA [Section 1.3.1]) and participant's tumor biopsy required for disease confirmation at baseline if archival tissue not available, and optional tumor biopsy at the EOT visit) will be collected from consenting participants.
- DNA samples will be used for research related to nirogacestat or desmoid and related diseases. They may also be used to develop tests/assays including diagnostic tests related to nirogacestat or treatments of this drug class and desmoid. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analyzed for the presence of known mutations. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to nirogacestat or study treatments of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on nirogacestat continues but no longer than 10 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study treatment • Report the event to the sponsor **within 24 hours** • Complete the liver event in the eCRF and complete the SAE eCRF form if the event also met the criteria for an SAE[2] • Perform liver chemistry follow-up assessments • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) • Restart/rechallenge is **not allowed per protocol and not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF page • Record use of concomitant medications (including

MONITORING: **<u>If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **<u>If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF page. • Record alcohol use on the liver event alcohol intake eCRF **<u>ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; eCRF = electronic case report form; HPLC = high performance liquid chromatography; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; SAE = serious adverse event; ULN = upper limit of normal;

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

Liver Chemistry Increased Monitoring Criteria with Continued Study Treatment

Liver Chemistry Increased Monitoring Criterion and Follow-Up	
Criterion	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the medical monitor within **24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

10.7. Appendix 7: Cytochrome P450 Inhibitors and Inducers

A listing of cytochrome P450 inhibitors and inducers can be found using the following link: http://medicine.iupui.edu/clinpharm/ddis/main-table

10.8. Appendix 8: Eastern Cooperative Oncology Group Performance

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655

10.9. Appendix 9: RECIST (Response Evaluation Criteria In Solid Tumors) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours:

Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

Categorizing lesions at Baseline:

- Only participants with measurable disease (i.e., at least one measurable lesion) at screening are included.

Measurable lesion – Lesion that can be accurately measured in at least one dimension (longest diameter (LD) in the plane of measurement is to be recorded) and with longest diameter at least twice the slice thickness and at least 10 mm when assessed by computed tomography (CT) or magnetic resonance imaging (MRI)

- Measurable disease will be assessed by CT or MRI.
- The same method of assessment (CT or MRI) and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up.
- Target Lesion--all measurable lesions up to maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline.
- Non-target Lesion--All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Methods of Measurement

CT or MRI must be used to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Recording Tumor Assessments

All sites of disease must be assessed at screening. Screening assessment should be done within 28 days of starting study treatment. For an adequate screening assessment, all required scans must be done within 28 days prior to first dose of study treatment and all disease must be documented appropriately. Participants must have progressive disease (PD) within a 12-month period prior to first dose of study treatment.

At follow-up, disease site must be assessed using the method (CT or MRI) and same technique as screening, including consistent administration of contrast (CT only) and timing of scanning. If a change needs to be made the case must be discussed with the sponsor.

Unequivocal new lesions will be recorded at follow-up time points. Measurement of new lesions is not required. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Response Criteria:

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions.
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of LD.
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of LD recorded since the treatment started or the appearance of one or more unequivocal new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria (defined below).

Time point response: patients with target disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Confirmation

- **Confirmation of progression:** assessment of PD will be confirmed and documented by an independent, blinded central radiological review Confirmation of response:
    - The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
    - To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.
- **Confirmation of SD:** in the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD

is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
    - The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specifies the minimal time interval required between two measurements for determination of SD. This time interval should consider the expected clinical benefit that such a status may bring to the population under study.

10.10. Appendix 10: Abbreviations

Abbreviation	Definition
AE	Adverse event(s)
ADL	Activities of daily living
ALT	Alanine aminotransferase
APC	Adenomatous polyposis coli
AST	Aspartate aminotransferase
BID	Twice daily
BPI	Brief pain inventory
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CPK	Creatine phosphokinase
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTNNB1	β-catenin
CYP3A4	Cytochrome P450 3A4
D-BIL	Direct bilirubin
DDI	Drug-drug interaction(s)
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid,
DT/AF	Desmoid tumors/aggressive fibromatosis
ECG	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form(s)
EDC	Electronic data capture
EFS	Event free survival
EOT	End of treatment
ePRO	Electronic patient report outcome
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin embedded
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase;
GS	Gamma-secretase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
Hes1	Hairy and enhancer of split-1
HGB	Hemoglobin
HIV	Human immunodeficiency virus

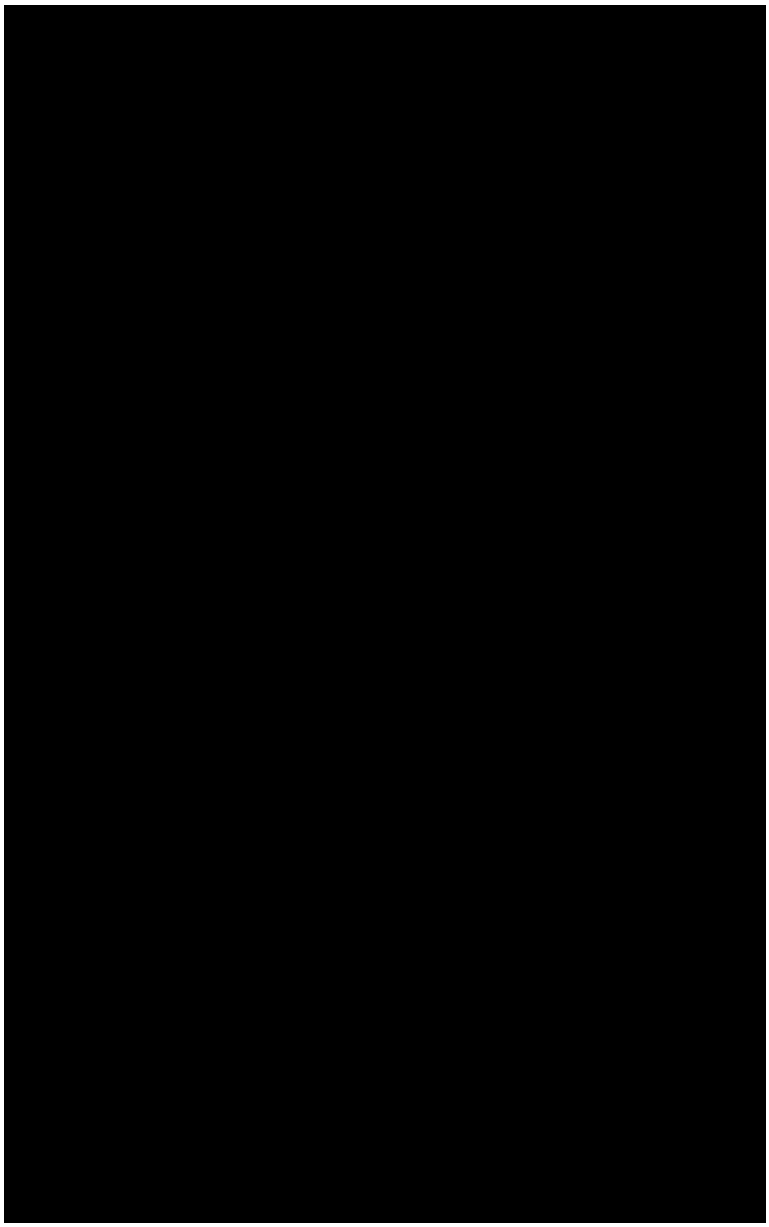
Abbreviation	Definition
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRT	Hormonal replacement therapy
ICF	Informed consent form(s)
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
LD	Longest diameter
LDH	Lactate dehydrogenase
MCH	Mean cell hemoglobin
MCV	Mean cell volume
MDASI	MD Anderson Symptom Inventory
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NICD	Notch intracellular domain
NSAIDs	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetic(s)
PLT	Platelet
PR	Partial response
PRO	Patient report outcome
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of activities
STSs	Soft-tissue sarcomas

Abbreviation	Definition
TBIL	Total bilirubin
UBC	United BioSource LLC
ULN	Upper limit of normal
v	Version
WBCC	White blood cell count
WOCBP	Women of childbearing potential

11. Appendix 11: List of Contacts for Study

11.1.1. Sponsor

SpringWorks Therapeutics
575 5th Avenue
New York, NY 10017
United States
Telephone: 212-421-8012
Fax: 646-609-8816



12. References

Bo N, Wang D, et al. Analysis of β-catenin expression and exon 3 mutations in pediatric sporadic aggressive fibromatosis. Pediatr Dev Pathol. 2012 May Jun;15(3):173-8.

Casali PG, Abecassis N, et al.; ESMO Guidelines Committee and EURACAN. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; Epub ahead of print, May 28.

de Camargo VP, Keohan ML, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). Cancer. 2010 May 1;116(9):2258-65.

Eisenhaur EA, Therasse P, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Gounder, M., Mahoney M, et al. Phase III, randomized, double blind, placebo-controlled trial of sorafenib in desmoid tumors J Clin Oncol 36, 2018 (suppl; abstr 11500).

Hosalkar, H, Fox EJ, et al. Desmoid Tumors and Current Status of Management. Orthop Clin N Am 2006(37):53-63.

Janinis J, Patriki M, et al. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol. 2003 Feb;14(2):181-90.

Kasper B, Baumgarten C, et al.; Desmoid Working Group. Management of sporadic desmoid type fibromatosis: a European consensus approach based on patients' and professionals' expertise- a sarcoma patients EuroNet and European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative. Eur J Cancer. 2015 Jan;51(2):127 36.

Kasper B, Gruenwald V, et al. Imatinib induces sustained progression arrest in RECIST progressive desmoid tumours: Final results of a phase II study of the German Interdisciplinary Sarcoma Group (GISG). Eur J Cancer. 2017 May;76:60-67.

Kasper B, Ströbel P, et al. Desmoid tumors: clinical features and treatment options for advanced disease. Oncologist. 2011;16(5):682-93.

Klinakis A, Szabolcs M, et al. Myc is a Notch1 transcriptional target and a requisite for Notch1-induced mammary tumorigenesis in mice. Proc Natl Acad Sci USA. 2006 Jun 13;103(24):9262-67.

Kummar S, O'Sullivan Coyne G, et al. Clinical activity of the γ-secretase inhibitor PF-03084014 in adults with desmoid tumors (Aggressive Fibromatosis). J Clin Oncol. 2017 May 10;35(14):1561-69.

Lazar AJ, Tuvin D, et al. Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol. 2008 Nov;173(5):1518-27.

Lewis JJ, Boland PJ, et al. The enigma of desmoid tumors. Ann Surg. 1999 Jun;229(6):866-72.

Messersmith WA, Shapiro GI, et al. A Phase I, dose finding study in patients with advanced solid malignancies of the oral γ-secretase inhibitor PF-03084014. Clin Cancer Res. 2015 Jan 1;21(1):60-7.

Penel N, Le Cesne A, et al. Surgical versus non-surgical approach in primary desmoid-type fibromatosis patients: A nationwide prospective cohort from the French Sarcoma Group. Eur J Cancer. 2017 Sep;83:125-31.

Quintini C, Ward G, et al. Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg. 2012 Mar;255(3):511-6.

Rampazzo E, Persano L, et al. Wnt activation promotes neuronal differentiation of glioblastoma. Cell Death Dis. 2013 Feb 21;4:e500.

Rodilla V, Villanueva A, et al. Jagged1 is the pathological link between Wnt and Notch pathways in colorectal cancer. Proc Natl Acad Sci USA. 2009 Apr 14;106(15):6315-20.

Schöffski P, Requilé A, et al. Assessment of physician's systemic treatment preferences for patients with advanced desmoid-type fibromatosis: experience-based medicine in the absence of high-level evidence. Oncol Res Treat. 2018;41(4):214-19.

Shang H, Braggio D, et al. Targeting the Notch pathway: a potential therapeutic approach for desmoid tumors. Cancer. 2015 Nov 15;121(22):4088-96.

Sharma VM, Calvo JA, et al. Notch1 contributes to mouse T cell leukemia by directly inducing the expression of c-myc. Mol Cell Biol. 2006 Nov;26(21):8022-31.

Skubitz KM. Biology and Treatment of aggressive fibromatosis or desmoid tumor. Mayo Clin Proc. 2017 Jun;92(6):947-64.

Smith AJ, Lewis JJ, et al. Surgical management of intra-abdominal desmoid tumours. Br J Surg. 2000 May;87(5):608-13.

Tejpar S, Nollet F, et al. Predominance of beta-catenin mutations and beta-catenin dysregulation in sporadic aggressive fibromatosis (desmoid tumor). Oncogene. 1999 Nov 11;18(47):6615-20.

Ungerbäck J, Elander N, et al. The Notch-2 gene is regulated by Wnt signaling in cultured colorectal cancer cells. PLoS One. 2011 Mar 18;6(3):e17957.

Villalobos VM, Hall F, et al. Long-term follow-up of desmoid fibromatosis treated with PF-03084014, an oral gamma secretase inhibitor. Ann Surg Oncol. 2018 Mar;25(3):768-75.

TITLE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Protocol Number: NIR-DT-301

Amendment Number: 5

Compound Number: PF-03084014 (nirogacestat)

Study Phase: Phase 3

Short Title: A Placebo-Controlled, Phase 3 Study of Nirogacestat in Adults with Desmoid Tumor/Aggressive Fibromatosis (DT/AF).

Acronym: DeFi

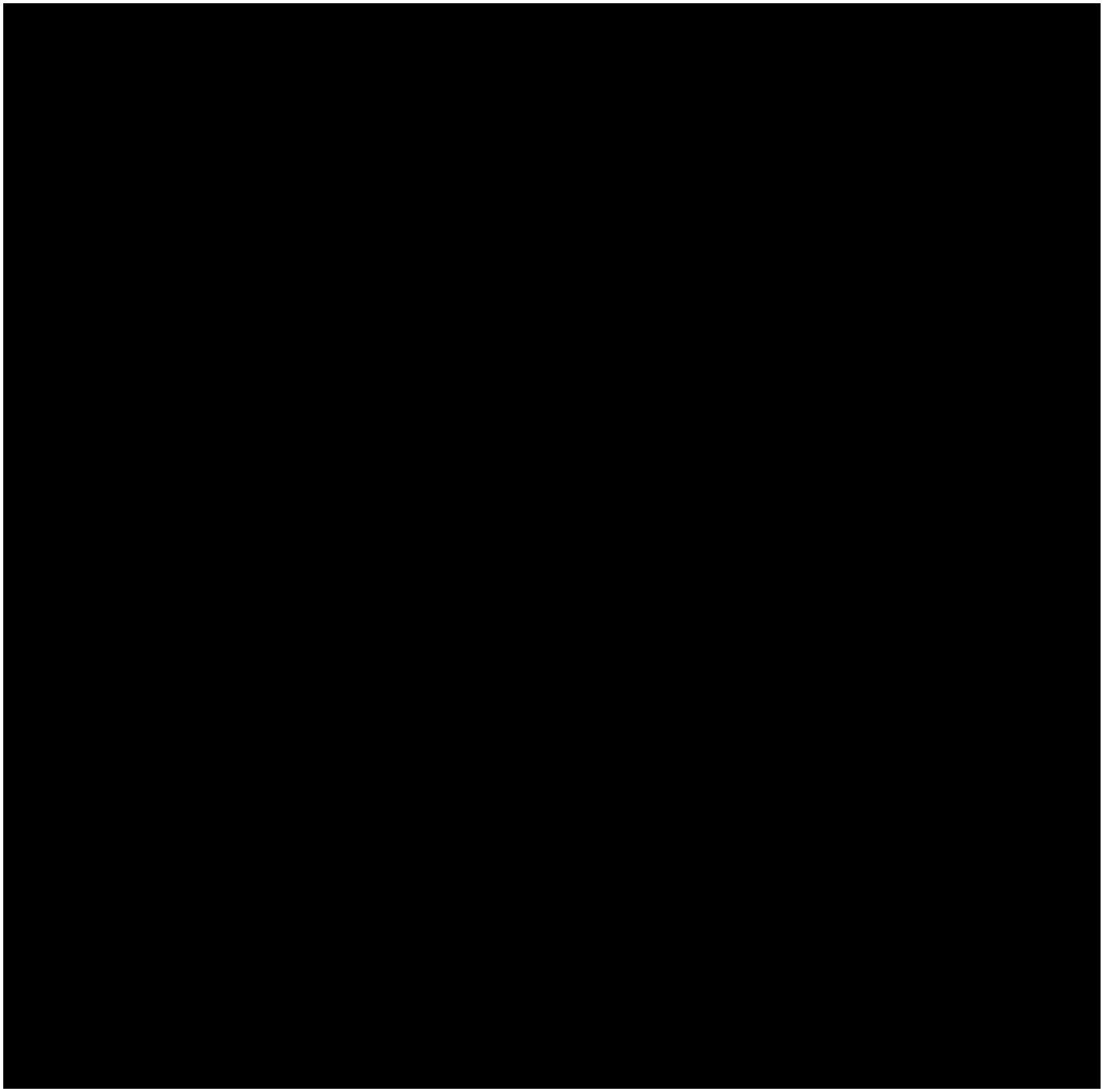
Sponsor Name: SpringWorks Therapeutics
Legal Registered Address: 100 Washington Blvd, Stamford, CT 06902, United States

Regulatory Agency Identifier Number(s)

Registry	ID
EudraCT	2018-001991-39
IND	138207

Approval Date: 09 February 2021

Confidentiality Statement



Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Date**	**Comment**
Amendment 5	09 February 2021	Global
Amendment 4	07 July 2020	Not implemented and not released to sites
Amendment 3	27 January 2020	Global
Amendment 2 / CAN-2.1	04 February 2020	Canada only
Amendment 2 / GBR-2.2	17 January 2020	Great Britain only
Amendment 2	14 October 2019	Global
Amendment 1 / ITA-1	19 March 2019	Italy only
Amendment 1	27 November 2018	Global
Original Protocol	03 August 2018	Global

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Short Title: A Placebo-Controlled, Phase 3 Study of Nirogacestat in Adults with Desmoid Tumor/Aggressive Fibromatosis (DT/AF).

Rationale:
The NIR-DT-301 Phase 3, double-blind, placebo-controlled study is being conducted to determine the efficacy and safety of nirogacestat in participants with progressing desmoid tumors. A Phase 1 solid tumor study provided preliminary efficacy (Messersmith, 2015), including long-term durable responses and safety of nirogacestat in desmoid participants (Villalobos, 2018). These encouraging results led to a Phase 2 study in participants with progressing desmoid tumors (Kummar, 2017). This study demonstrated that nirogacestat resulted in a 29% response rate, significant tumor shrinkage as measured by magnetic resonance imaging (MRI) and no participants progressed while on therapy. Importantly, participants in the responder group had failed previous systemic therapies (imatinib or sorafenib) indicating a need for alterative therapeutic options for this patient population. These results support the further study of nirogacestat in this population.

Objectives and Endpoints

Key Objectives	**Key Endpoints**
Primary	**Primary**
To determine the efficacy (as defined by progression-free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF.	PFS defined as the time from randomization until the date of assessment of progression or death by any cause will be determined. Progression will be determined radiographically using Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1 (Eisenhauer, 2009; Section 10.8) or clinically as assessed by the investigator. Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.

Key Objectives	**Key Endpoints**
Secondary	**Secondary**
To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of adverse events (AEs);	Safety endpoints will include incidence of treatment-emergent AEs, changes in laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs). Tolerability will be assessed according to toxicities graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0;
To determine the overall response rate (complete response [CR] + partial response [PR]) of nirogacestat in participants with progressing DT/AF;	Overall response rate, defined as the proportion of participants with CR + PR assessed via central reader using RECIST v1.1 Criteria;
To determine the duration of response;	Duration of response for participants whose best response is CR or PR;
To compare tumor volume changes measured by MRI in participants with progressing DT/AF; and	Change in tumor volume from baseline as assessed by MRI volumetric; and
To evaluate desmoid tumor symptoms and impacts using patient-reported outcomes (PROs).	Symptoms and impacts will be assessed by evaluating change from baseline on the following PROs: • GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS); • Brief Pain Inventory (BPI) short form; • Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks; and • European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30.

Overall Design:
This is a multi-center, randomized, double-blind, placebo-controlled, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. This study will consist of 2 phases, a double-blind and an optional open-label extension (OLE) phase.

Participants will be screened up to 28 days prior to the first dose of study treatment (nirogacestat or placebo) in the double-blind phase and eligibility will be based on the inclusion and exclusion criteria (Sections 5.1 and 5.2). Refer to the double-blind schedule of activities (SoA) (Section 1.3.1) for the required assessments and Table 6 for additional details regarding each scheduled study visit.

If Central Imaging Review determines that a participant has progressive disease (using RECIST v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will return to the site for an end of treatment (EOT) visit within 14 days of the notification. During the EOT visit, the participant will be unblinded and have the option to enter the OLE phase, if eligible (Section 6.7.1).

Participants who discontinue due to reasons other than radiographic disease progression as determined via central review will not be unblinded and will not be eligible for participation in the optional OLE phase of the study.

At the completion of the double-blind phase (once the required number of events have been observed and the primary PFS analysis has been completed), the remaining participants in the double-blind phase will have their study treatment assignment unblinded and if eligible, will have the option to enroll in the optional OLE phase (Section 6.7.1). Refer to OLE SoA (Section 1.3.2) for the required assessments and for additional details regarding each scheduled study visit.

See Section 1.2 for study schema.

Disclosure Statement: This is a randomized, parallel treatment study with 2 arms that is participant and investigator blinded. There is an optional OLE phase for eligible participants.

Number of Participants:
Approximately 135 participants will be screened (assessed for eligibility) to achieve 118 participants randomly assigned (1:1) to study treatment (placebo or nirogacestat). It is estimated that 51 observed progression events will be needed to meet the primary PFS analysis. Refer to Section 9.2 for sample size determination.

Treatment Groups and Duration:
Double-blind phase:

At Cycle 1 Day 1 (baseline), participants will be randomized (stratified by primary tumor location [Section 6.3.1]) to study treatment (nirogacestat or placebo) in a 1:1 ratio and will receive 150 mg twice daily (BID) of study treatment, continuously in 28-day cycles. Participants

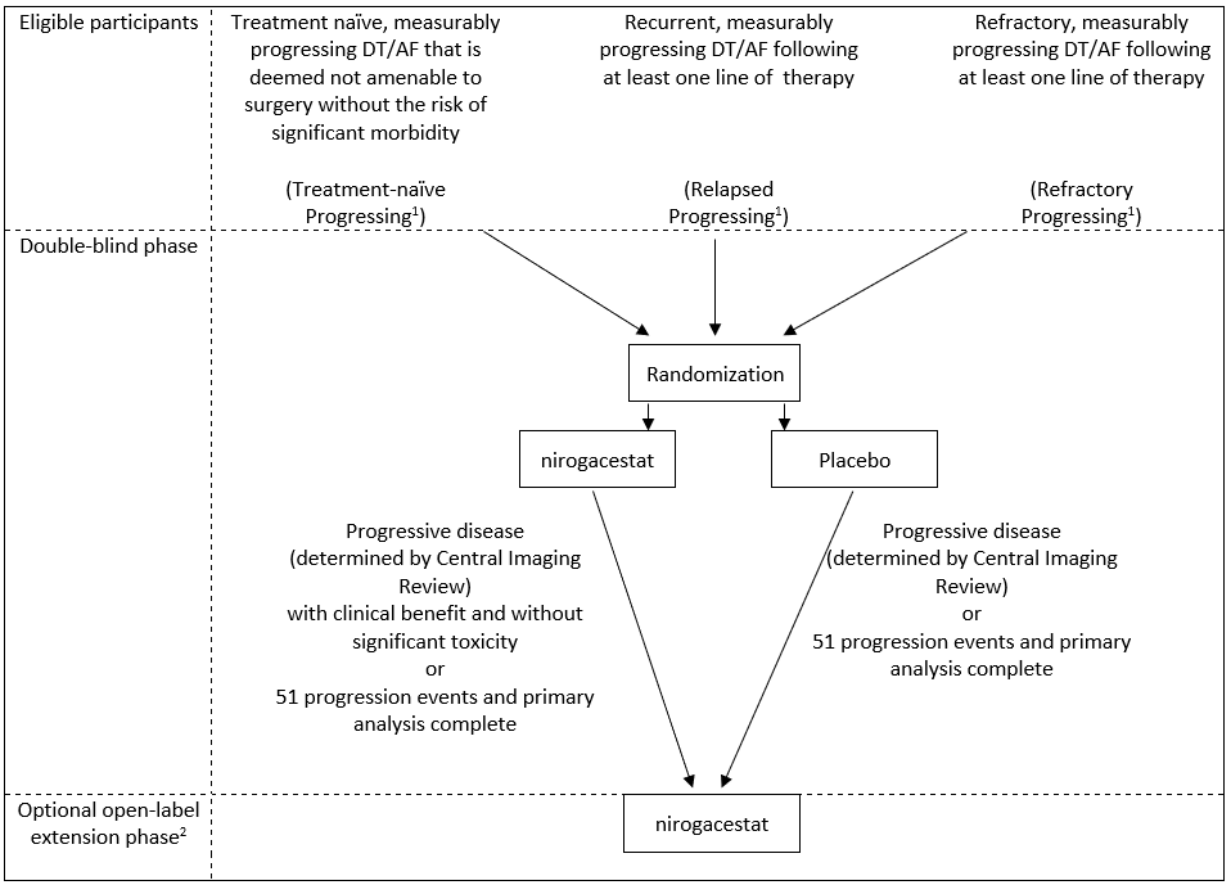
will remain in the double-blind phase until death, disease progression, they prematurely discontinue study treatment for any reason, the study is stopped by the sponsor for any reason, or the required number of PFS events have been observed and the primary PFS analysis has been completed (based on current statistical assumptions, this is anticipated to be approximately 2 years after the first participant is randomized).

Open-label phase:

Eligible participants (refer to Sections 6.7.2 and 6.7.3 for OLE eligibility criteria) may enroll in the optional OLE phase to receive 150 mg BID of nirogacestat (open-label study treatment), continuously in 28-day cycles. Participants will remain in the OLE phase until death, disease progression, they prematurely discontinue study treatment for any reason, the study is stopped by the sponsor for any reason, participant qualifies for Sponsor's Continued Access Plan, or nirogacestat is commercially available.

Data Monitoring Committee: Yes

1.2. Schema



DT/AF = desmoid tumor/aggressive fibromatosis.

[1]All eligible participants must have histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan (inclusion criteria 2).

[2]Participants discontinuing study treatment due to clinical progression are not eligible for participation in the OLE.

1.3. Schedule of Activities (SoA)

1.3.1. Double-Blind Phase SoA

Double-Blind Phase Cycle Number	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(±2 days)*	**Week 3** *Day 15* *(±2 days)*	**Week 4** *Day 22* *(±2 days)*	**Week 8** *Day 56* *(±2 days)*	**Week 13** *Day 85* *(±7 days)*	**Week 25 & On** *Day 169 & On* *(±7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Informed consent[2]	X									
I/E criteria	X	X								
Demography	X									
Medical history including menstrual history for women	X									
ECOG performance status[4]	X	X				X	X	X	X	X
Physical examination[5]	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X
Weight/height[7]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[8]	X	X[8a] *(pre-& post dose)*	X[8b] *(post dose)*			X	X	X	X	X
Laboratory										
Tumor biopsy[9]	X[9a]								X[9b] *(optional)*	
Blood for serology[10]	X									
Blood for serum pregnancy test (WOCBP only)[11]	X									
Blood for PK sampling[12]		X[12a] *(serial)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*		
Blood for pharmacogenomics[13]		X *(optional)*								
Blood for genotyping[14]		X								
Blood for safety labs[15]	X	X	X	X	X	X	X	X	X	X

Double-Blind Phase Cycle Number	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(±2 days)*	**Week 3** *Day 15* *(±2 days)*	**Week 4** *Day 22* *(±2 days)*	**Week 8** *Day 56* *(±2 days)*	**Week 13** *Day 85* *(±7 days)*	**Week 25 & On** *Day 169 & On* *(±7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Blood for female hormone levels[15]	X	X			X	X	X	X	X	X
Blood for male hormone levels[15]		X					X	X	X	X
Urinalysis[16]	X	X				X	X	X	X	X
Urine pregnancy test (WOCBP only)[17]		X			X	X	← *(monthly)[17a]* →		X	X
Patient-Reported Outcomes (PROs)[18]										
Home ePRO device training	X									
GODDESS (symptom scale)	← *(refer to Table 8)* →					← *(monthly assessment, refer to Table 8)* →				← *(refer to Table 8)* →
BPI short form										
PROMIS PF short form 10a plus 3 additional items from PROMIS item banks										
GODDESS (impact scale)										
EORTC QLQ-C30										
PGIS										
PGIC										
Imaging and RECIST										
Pre-Randomization RECIST v1.1 Calculation Worksheet[19]	X									
CT or MRI scan for tumor measurement (using RECIST v1.1)[20]	X[20a]						X[20b]	X[20b]	X[20c]	
MRI scan for tumor volume assessment[20]	X							X[20b] *(every 6 cycles)*	X[20c]	
Local RECIST v1.1 read[20]	X[20a]						X	X[20b]	X[20c]	

Double-Blind Phase Cycle Number	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(±2 days)*	**Week 3** *Day 15* *(±2 days)*	**Week 4** *Day 22* *(±2 days)*	**Week 8** *Day 56* *(±2 days)*	**Week 13** *Day 85* *(±7 days)*	**Week 25 & On** *Day 169 & On* *(±7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Enrollment and Study Treatment										
Randomization[21]		X								
Study treatment dispensing[22]		X					X	X		
Study treatment administration/diary[23]		←	—	—	—	—	—	→		
Study treatment accountability							X	X	X	
Ongoing Monitoring										
Monthly wellness checks[24]	←	—	—	—	—	—	—	→		
ConMed review	←	—	—	—	—	—	—	—	—	→
AE/SAE review[25]	←	—	—	—	—	—	—	—	—	→

AE = adverse event; BID = twice daily; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = end of treatment; ePRO = electronic patient-reported outcome; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; ICF = informed consent form; I/E = inclusion/exclusion; IRT = interactive response technology; MRI = magnetic resonance imaging; OLE = open-label extension; PFS = progression free survival; PGIS = patient global impression of severity; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SoA = scheduled of activities; v = version; WOCBP = women of child bearing potential..

1. **Screening visit:** Assessments may occur up to 28 days prior to first dose of study treatment with a minimum screening period of 14 days to allow for participant completion of the screening and baseline PRO assessments (refer to Table 8 for PRO administration schedule). An extension to the screening period may be permitted on a case-by-case basis following discussion between the investigator and the medical monitor/sponsor. The reason(s) for the extension must be clearly documented.
2. **Informed consent process:** Includes participant signing the ICF and must be conducted prior to any study related procedures being performed. The date the participant signs the ICF will be Day 1 of the screening period. Refer to Section 10.1.3 for more detail on the ICF process.
3. **Baseline visit:** Assessments may be performed over a 48-hour period. All baseline assessments are to be conducted prior to first dose of study treatment except for the following assessments: post-dose 12-Lead ECGs and post-dose blood draws for pharmacokinetic (serial PK) sampling.
4. **ECOG performance status:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Section 10.7 for ECOG scale.

5. **Physical examination:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Section 8.2.2 for detail regarding physical examination requirements.
6. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature (following at least 5 minutes of rest). At baseline, assessment must be done prior to first dose of study treatment. Refer to Section 8.2.4 for more detail.
7. **Height:** Required at screening only. Weight to be collected at all visits.
8. **12-lead ECGs:** Will be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. Refer to Section 8.2.3 for more detail.

    8a. At baseline, triplicate ECGs are required at two timepoints: (1) prior to the first dose of study treatment and (2) approximately 1-hour post-dose.

    8b. At Cycle 1 Day 8, triplicate ECGs are required 1-hour (±10 minutes) post-dose.
9. **Tumor (core needle) biopsy:** If tumor biopsy and MRI are performed during the same study visit, the biopsy must be done after MRI. Refer to Section 8.1.3 and central laboratory manual for sample processing details.

    9a. At screening, tumor biopsy is only required if archival tissue is not available for study procedures. Tumor biopsy will be reviewed centrally to reconfirm diagnosis, but participant enrollment is not dependent on central review.

    9b. At EOT, tumor biopsy will be optional and additional pharmacogenomic consenting is required (10.1.3).
10. **Serology:** Only required at screening and to include testing for hepatitis B virus (hepatitis B surface antigen), hepatitis C virus (hepatitis C antibody [Hepatitis C virus polymerase chain reaction, if hepatitis C antibody positive]), and human immunodeficiency virus. Refer to Section 10.2 and central laboratory manual for sample processing details.
11. **Serum pregnancy test:** Only required at screening for women of childbearing potential (WOCBP). Refer to Sections 8.3.5 and 10.4, and central laboratory manual for sample processing details.
12. **PK sampling:** Refer to Section 8.5 and Table 11, and central laboratory manual for sample processing details.

    12a. Serial PK: Required on Cycle 1 Day 1 at the following timepoints: pre-dose and 0.25-, 0.5-, 1-, 1.5-, 2- and 3-hours post-dose. All efforts will be made to obtain the sample within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing. Out of window PK draws will not be captured as deviations if the exact time of the sample collection is noted on the source documents and eCRF.

    12b. Trough PK: The evening before applicable study visits, participants will record the exact time study treatment was taken in the eDiary using the home ePRO device. Participants will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.
13. **Pharmacogenomics:** Blood sample will be optional and additional pharmacogenomic consenting is required (Section 10.1.3). At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Sections 8.8 and 10.5, and central laboratory manual for sample processing details.
14. **Genotyping:** Required blood sample for all participants unless prohibited by local regulations. At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Section 8.7 and central laboratory manual for sample processing details.

15. **Safety Labs (hematology, serum chemistry, and hormone levels):** At baseline, must be done prior to first dose of study treatment. Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. The time of hormone level blood draws should also be recorded.

16. **Urinalysis:** At baseline, must be done prior to first dose of study treatment. Refer to Section 10.2 for a complete list of analytes and the central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results and only if blood or protein is abnormal.

17. **Urine pregnancy tests:** Only required for WOCBP. At baseline, urine pregnancy test must be done prior to first dose of study treatment to reconfirm eligibility. Refer to Sections 8.2.6 and 10.4 for more detail.

    17a. Following the Cycle 4 Day 1 study visit, all WOCBP participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to the study reference manual for additional details).

18. **PROs:** Participants will complete the questionnaires and record study treatment administration in the eDiary using a home ePRO device (Section 8.1.2). Refer to Table 8 for the PRO administration schedule.

19. **Pre-Randomization RECIST v1.1 Calculation Worksheet** (Section 8.1.1.1): As part of documenting that participants have satisfied inclusion criteria 2, sites are required to complete a worksheet (provided by the sponsor). The worksheet must be submitted to the sponsor's designee during the screening period as soon as the data are available to complete the worksheet. All worksheets must be received no later than 7 days prior to C1D1 to allow for review prior to randomization (refer to study reference manual for additional details).

20. **Tumor imaging:** All scans will be submitted to the central imaging core laboratory and read by Central Imaging Review throughout the study. Refer to Section 8.1.1and imaging manuals for more detail.

    Tumor measurement using RECIST v1.1 assessment (Section 8.1.1.2): CT scans (contrast required unless contraindicated) or MRI scans (no contrast required) will be acquired to assess tumor changes. The modality (CT or MRI) for tumor assessment is to be determined by the investigator. The imaging modality used to assess the tumor at screening must be used at each subsequent visit. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review, but participant enrollment is not dependent on central review. Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.

    Tumor volumetric assessment (Section 8.1.1.3)**:** MRI scans (no contrast required) will be acquired to assess tumor volume. All scans will be submitted to the central imaging core laboratory and assessed by Central Imaging Review.

    If applicable, CT and MRI assessments may be conducted on the same day. However, MRI with no contrast must be performed prior to CT with contrast. MRI must be done prior to tumor biopsy if assessments occur on the same visit.

    20a. Screening visit scans:

    - MRI and CT scans obtained during the screening visit will serve as the participant's baseline scan for the study (CT scan only required if it's the chosen modality for RECIST v1.1 tumor measurement). Scans should be submitted to central imaging core laboratory as early in the screening period as possible to confirm scan quality is acceptable for analysis prior to randomization.
    - Standard of care scan(s) acquired prior to the participant signing ICF may be used as the participant's screening visit scan(s) if obtained within 28 days of the first dose of study treatment and the quality of the scans are acceptable for analysis (as determined by the central

imaging core laboratory). These scans will then be collected, stored, and documented as the screening visit scan(s). No other pre-enrollment images will be collected for central reading.

20b. On study treatment scans: Starting at cycle 4, MRI or CT scans for tumor assessment (RECIST v1.1) will be obtained every 3 cycles. Starting at cycle 7, MRI for tumor volume assessment will be obtained every 6 cycles.

20c. EOT visit scans: only required if not performed within the past 3 months.

21. **Randomization:** Participants will not be randomized to study treatment using IRT until all I/E criteria (Sections 5.1 and 5.2) have been confirmed and all pre-randomization baseline study assessments have been completed.
22. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles at applicable study visits.
23. **Study treatment administration/diary:** The first dose of study treatment (3 × 50 mg tablets) will be administered orally at the site at Cycle 1 Day 1 followed by a 3-hour observation period. Participants will administer study treatment at 150 mg (3 × 50 mg tablets) twice daily (BID) (approximately every 12 hours, without regard to food) continuously in 28-day cycles throughout the study. Participants should record daily administration of each study treatment dose in the eDiary using the home ePRO device. Refer to Section 6.1 for more detail.
24. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit). Refer to Section 8.2.7 for more detail.
25. **AEs/SAEs:** Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail. Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).
26. **Every 3 cycles and on:** Following Cycle 7 Day 1, participants will return every 3 cycles for study visits until death, progressive disease, discontinuation of study treatment for any reason, study is stopped by the sponsor for any reason, or required number of PFS events have been observed and primary PFS analysis has been completed.
27. **EOT visit:** EOT visit should be conducted prior to study treatment discontinuation to avoid a gap in study treatment for participants entering the OLE phase. All EOT assessments must be conducted prior to unblinding (if applicable refer to Section 6.3.2.1).

    If Central Imaging Review determines that a participant has progressive disease (using RECIST v1.1) the participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (but no later than 14 days of becoming aware of the progression).

    If the participant discontinues study treatment for any reason other than progressive disease (as determined by Central Imaging Review using RECIST v1.1), they will be encouraged to return to the site as soon as possible to complete the EOT visit assessments prior to study treatment discontinuation or as close as possible to the last dose of study treatment.
28. **Follow-up visit:** Only required for participants who are not continuing into the optional OLE phase and will occur 30 days (+7 days) after the last dose of study treatment.

1.3.2. Open-Label Extension Phase SoA

OLE Phase **Cycle Number**	**Cycle 1**[5] *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2**[5]	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT**[20]	**Follow-Up**[21]
Cycle Day	**Day 1 Baseline**[3]	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(±2 days)*	**Week 3** *Day 15* *(±2 days)*	**Week 4** *Day 22* *(±2 days)*	**Week 8** *Day 56* *(±2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(±7 days)*	**Week 49 & On** *Day 337 & On* *(±7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Informed consent[1]	X								
I/E criteria[2]	X								
ECOG performance status[6]	*Same as double-blind EOT*				X	X	X	X	X
Physical examination[7]	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
Vital signs[8]	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
Weight	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
12-lead ECG[9]	X[9a] *(post dose)*	X[9b] *(post dose)*			X	X	X	X	X
Laboratory									
Blood for PK sampling[10]	X *(serial)*[10a]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]		
Blood for safety labs[11]	X[11a]	X	X	X	X	X	X	X	X
Blood for female hormone levels[11]	X[11a]			X	X	X	X	X	X
Blood for male hormone levels[11]	X[11a]					X	X	X	X
Urinalysis[12]	*Same as double-blind EOT*				X	X	X	X	X

OLE Phase **Cycle Number**	**Cycle 1**[5] *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2**[5]	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT**[20]	**Follow-Up**[21]
Cycle Day	**Day 1 Baseline**[3]	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(±2 days)*	**Week 3** *Day 15* *(±2 days)*	**Week 4** *Day 22* *(±2 days)*	**Week 8** *Day 56* *(±2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(±7 days)*	**Week 49 & On** *Day 337 & On* *(±7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Urine pregnancy test (WOCBP only)[13]	*Same as double-blind EOT*			X	X	← *(Monthly)*[13a] →		X	X
Patient-Reported Outcomes (PROs)[14]									
GODDESS (symptom scale)					*(Monthly assessment, refer to Table 9)*		*(Quarterly assessment, refer to Table 9)*		*(Refer to Table 9)*
BPI short form									
PROMIS PF short form 10a plus 3 additional items from PROMIS item banks									
GODDESS (impact scale)									
EORTC QLQ-C30									
PGIS									
PGIC									
Imaging and RECIST									
CT or MRI scan for tumor measurement (using RECIST v1.1)[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	
Local RECIST v1.1 read[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	
Enrollment and Study Treatment									
Enrollment/first dose of open-label study treatment[4]	X								
Study treatment dispensing[16]	X					X	X		

OLE Phase **Cycle Number**	**Cycle 1**[5] *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2**[5]	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT**[20]	**Follow-Up**[21]
Cycle Day	**Day 1 Baseline**[3]	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(±2 days)*	**Week 3** *Day 15* *(±2 days)*	**Week 4** *Day 22* *(±2 days)*	**Week 8** *Day 56* *(±2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(±7 days)*	**Week 49 & On** *Day 337 & On* *(±7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Study treatment administration/diary[17]	←	—	—	—	—	—	→		
Study treatment accountability						X	X	X	
Ongoing Monitoring									
Monthly wellness checks[18]	←	—	—	—	—	—	→		
ConMed review	←	—	—	—	—	—	—	—	→
AE/SAE review[19]	←	—	—	—	—	—	—	—	→

AE = adverse event; BID = twice daily; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = end of treatment; ePRO = electronic patient-reported outcome; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; ICF = informed consent form; I/E = inclusion/exclusion; IRT = interactive response technology; MRI = magnetic resonance imaging; OLE = open-label extension; PFS = progression free survival; PGIS = patient global impression of severity; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SoA = scheduled of activities; v = version; WOCBP = women of child bearing potential.

1. **Informed consent process:** Includes participant signing the ICF (exclusive to the OLE study phase) and must be conducted prior to administration of the first dose of open-label study treatment. Refer to Section 10.1.3 for more detail on the process.
2. **I/E criteria:** Exclusive to the OLE phase. Refer to Sections 6.7.2 and 6.7.3 for participant eligibility criteria specific to the OLE phase.
3. **Baseline visit:** The C1D1 visit of the OLE phase should be conducted on the same day as, or within 24 hours after, the double-blind EOT visit. A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1. All double-blind EOT visit assessments, as described in the double-blind SoA (Section 1.3.1), will be conducted **prior** to unblinding the participant's study treatment and prior to administration of the first dose of open-label study treatment.
4. **Enrollment and first dose of open-label study treatment:** Participants will be enrolled in the OLE phase using the IRT only after (1) all ongoing AEs/SAEs from the double-blind phase have been assessed for causality in a blinded manner by the investigator or qualified designee, and (2) all AE/SAE causality assessments have been entered into the eCRF. All double-blind EOT visit assessments must be completed **prior** to unblinding and taking first dose of open-label study treatment.

Participants who were randomized to receive placebo in the double-blind phase will receive their first dose of study treatment at the site followed by a 3-hour observation period.

Participants who were randomized to nirogacestat in the double-blind phase may take their first dose of open-label study treatment at home (observation period is not required).

5. **Study visits at Cycle 1 (Day 8, 15 and 22) and Cycle 2 (Day 28):** Only applicable for participants who were previously randomized to receive placebo in the double-blind phase. If a participant was randomized to receive nirogacestat in the double-blind phase, these study visits will not be conducted, and the participant will not be required to return to the site until Cycle 4 Day 1 visit.
6. **ECOG performance status:** Refer to Section 10.7 for the ECOG scale.
7. **Physical examination:** Refer to Section 8.2.2 for more detail regarding physical examination requirements.
8. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature (following at least 5 minutes of rest). Refer to Section 8.2.4 for more detail.
9. **12-lead ECGs:** Will be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. Refer to Section 8.2.3 for more detail.

    9a. At baseline, triplicate ECGs are required approximately 1-hour post-dose (open-label study treatment). Applicable only to participants who were previously randomized to receive placebo in the double-blind study phase.

    9b. At Cycle 1 Day 8 visit, triplicate ECGs are required 1-hour (±10 minutes) post-dose. Applicable to participants who were previously randomized to receive placebo in the double-blind study phase only.

10. **PK sampling:** Refer to Section 8.5 and central laboratory manual for sample processing details.

    10a. Serial PK: Only applicable to participants who were previously randomized to receive placebo in the double-blind study phase. PK samples should be collected on OLE Cycle 1 Day 1 at the following timepoints: pre-dose and 0.25-, 0.5-, 1-, 1.5-, 2- and 3-hours post-dose. All efforts will be made to obtain within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing. Out of window PK draws will not be captured as deviations if the exact time of the sample collection is noted on the source documents and eCRF.

    10b. Trough PK: The evening before applicable study visit, participants will record the exact time study treatment was taken in the eDiary using the home ePRO device. Participants will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.

11. **Safety labs (hematology, serum chemistry, and hormone levels):** Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. The time of hormone level blood draws should also be recorded.

    11a. At baseline, blood draws for hematology, serum chemistry, and hormone levels will be done as part of the double-blind EOT visit (prior to unblinding). However, if hematology and serum chemistry safety labs have not been conducted within the 14 days prior to C1D1, an additional blood draw will be required for same day local laboratory processing to reconfirm adequate organ and bone marrow function (refer to OLE inclusion criteria 2) and must be done prior to first dose of open-label study treatment.

12. **Urinalysis:** Refer to Section 10.2 for a complete list of analytes and the central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results and only if blood or protein is abnormal.

13. **Urine pregnancy tests:** Only required for WOCBP. Refer to Sections 8.2.6 and 10.4 for more detail.

    13a. Following Cycle 4 Day 1 study visit, all WOCBP participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to study reference manual for additional details).

14. **PROs:** Participants will complete the questionnaires using a home ePRO device (Section 8.1.2). Refer to Table 9 for the PRO administration schedule.

15. **Tumor imaging:** CT (contrast required unless contraindicated) or MRI (no contrast required) using RECIST v1.1 (modality to be determined by the investigator) is required. Whichever imaging modality is used to measure the tumor by RECIST v1.1 at screening in the double-blind phase must be used at each subsequent visit throughout the OLE phase. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review. Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.

    15a. Scan is required every 3 cycles until Cycle 13 Day 1, and then every 6 cycles thereafter.

    15b. At EOT, scan is only required if not performed within the past 3 months.

16. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles during study visits.

17. **Study treatment administration/diary:** Participants will self-administer study treatment at 150 mg (3 × 50 mg tablets) BID (approximately every 12 hours, without regard to food), continuously in 28-day cycles throughout the study. Participants should record daily administration of each study treatment dose in the eDiary using the home ePRO device. (Section 6.1).

18. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit). Refer to Section 8.2.7 for more detail.

19. **AEs/SAEs:** Will be monitored and documented from the time of informed consent and up to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail. Females reporting AEs/AESIs/SAEs of POI and/or amenorrhea will have hormone levels assessed every three months until event resolution (or for at least 90 days after discontinuing study treatment).

20. **End of treatment (EOT) visit:** Should be conducted prior to study treatment discontinuation or as close as possible to the last dose of open-label study treatment.

21. **Follow-up visit:** Only required for participants who are not transitioning directly to commercial nirogacestat (or sponsor's Continued Access Plan) at time of discontinuation. The follow-up visit will occur 30 days (+7 days) after the last dose of study treatment.

2. INTRODUCTION

Nirogacestat (PF-03084014) is a potent, small-molecule, selective, reversible, noncompetitive inhibitor of gamma secretase (GS). Nirogacestat is being investigated for the treatment of desmoid tumors/aggressive fibromatosis (DT/AF).

2.1. Study Rationale

The NIR-DT-301 Phase 3, double-blind, placebo-controlled study is being conducted to determine the efficacy and safety of nirogacestat in participants with progressing desmoid tumors. A Phase 1 study in patients with solid tumors provided preliminary efficacy (Messersmith, 2015), including long-term durable responses and safety of nirogacestat in desmoid participants (Villalobos, 2018). These encouraging results lead to a Phase 2 study in participants with progressing desmoid tumors (Kummar, 2017). This study demonstrated that nirogacestat resulted in a 29% response rate, significant tumor shrinkage as measured by magnetic resonance imaging (MRI) and no participants progressing while on therapy. Importantly, participants in the responder group had failed previous systemic therapies (imatinib or sorafenib) indicating a need for alterative therapeutic options for this patient population. These results support the further study of nirogacestat in this population.

2.2. Background

2.2.1. Desmoid Tumors/Aggressive Fibromatosis

Desmoid tumors, also referred to as aggressive fibromatosis, are rare, locally invasive, slow growing soft tissue tumors. According to the World Health Organization, desmoid tumors are defined as “clonal fibroblastic proliferations that arise in the deep soft tissue and are characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize” (Kasper, 2011). Desmoid tumors are considered benign; however, they cause significant morbidity by infiltrating or exerting mass effects on vital structures (Lewis, 1999; Smith, 2000). Desmoid tumors include soft tissue masses arising in any part of the body in different varieties of connective tissue, including muscle and fascia aponeurosis. The most common primary tumor sites include abdominal walls, limbs, girdles, and mesenteric areas. Desmoid tumors infiltrate surrounding structures and spread along plains and muscle, which can lead to severe pain, functional impairment, and more rarely, life-threatening conditions (Penel, 2017). Despite the benign nature of desmoid tumors, they can behave aggressively, causing significant morbidity, with elevated rates of local recurrence (as high as 60%) despite wide excisions (Penel, 2017). Mortality is occasionally observed owing to the local aggressive nature of some desmoid tumors that occur in the mesentery (Smith, 2000).

Desmoid tumors most commonly occur in individuals between the ages of 15 to 60 years, more often in young adults, with the peak age of about 30 years, and a 2- to 3-fold predominance in females (de Camargo, 2010; Skubitz, 2017). The incidence of desmoid tumors is about 2 to 4 cases per million per year in the general population, with fewer than 1000 cases diagnosed in the United States per year (Hosalkar, 2006).

The incidence of desmoid tumors is reported to be about 800- to 1000-fold higher in patients with familial adenomatous polyposis (FAP [Gardner Syndrome]), in which the adenomatous polyposis coli (APC) tumor suppressor gene is mutated (Skubitz, 2017). Familial adenomatous polyposis-associated desmoid tumor is more frequently associated with abdominal tumors, especially in the Gardner variant of FAP, which is associated with intestinal polyposis, osteomas, fibromas, and epidermal inclusion cysts (Skubitz, 2017). Intra-abdominal desmoid tumors are one of the leading causes of death in patients with FAP (Quintini, 2012). Although common in patients with FAP, most cases of desmoid tumors occur spontaneously in adults and are associated with a mutation in β-catenin (CTNNB1) (Lazar, 2008; Tejpar, 1999; Bo, 2012). β-catenin is an integral component of the Wnt/β-catenin/T-cell transcription factor signaling pathway, which is frequently dysregulated in cancer. Patients with desmoid tumors carrying β-catenin have a worse 5-year recurrence-free survival rate than patients with wild-type tumors (Kummar, 2017).

Histologically, desmoid tumors appear as poorly circumscribed proliferation of myofibroblastic cells with variable collagen deposition, and tumor margins are difficult to assess at the time of surgery. Desmoid tumors are morphologically heterogeneous and may exhibit striking morphological intratumoral and intertumoral heterogeneity (Skubitz, 2017). In some areas, tumors may resemble fibroblasts of inactive fibrous tissue, whereas other areas may resemble the active fibroblasts of wound healing.

The clinical course of desmoid tumor may be unusual and heterogeneous, characterized not only by tumor growth, proliferation, and disease progression, but also by stabilization and spontaneous remission (Kasper, 2011). Desmoid tumors can present almost anywhere throughout the body, and there are different factors by which desmoid tumors develop. They can have wide range of clinical symptoms, such as bloating, pain, or rectal bleeding, in the case of abdominal desmoid tumors; or extremity pain, decreased range of motion, and swelling, in the case of extremity desmoid tumors. Given the heterogeneity of desmoid tumor, predicting the desmoid tumor behavior and determining which treatment option is appropriate for a patient remains challenging.

2.2.2. Diagnosis

There are several guidelines published on diagnosis, treatment, and follow-up of participants with soft tissue sarcomas (STS), including desmoid tumors. According to the clinical practice guidelines published in 2018 by the European Sarcoma Network Working Group, the basic principles for the diagnosis of STS applies to desmoid tumors (Casali, 2018). Because of the ubiquitous nature of sarcomas and their site of origin, a multidisciplinary (e.g., radiologist, pathologist, surgeon, medical oncologist, etc.) approach to the diagnosis and management is warranted. Once a sarcoma mass is suspected, non-invasive imaging by MRI or computed tomography (CT) is performed. Additionally, a biopsy is performed, if feasible. Once the primary diagnosis of desmoid tumor is confirmed, the potential treatment options outlined below are evaluated.

2.2.3. Treatment

Treatment options vary for each patient depending on the size, location and morbidity associated with the tumor. The wait-and-see policy is currently recommended as the first approach in desmoid tumors (Kasper, 2015). In a prospective study comparing surgical versus non-surgical approaches in primary desmoid tumors conducted by the French Sarcoma Group (Penel, 2017), the wait-and-see policy was implemented regardless of primary tumor location. For all patients, the 2-year event free survival (EFS) rate was 56%. The 2-year EFS was 63% and 70% for patients managed by wait-and-see approach and for surgery with tumors in favorable locations (abdominal wall, intra-abdominal, breast, digestive viscera and lower limb), respectively. However, in patients with unfavorable tumor locations (chest wall, head and neck, upper limb) the 2-year EFS was significantly improved in participants initially managed with the wait-and-see approach (52%) vs surgery (25%). The authors concluded that the wait-and-see approach may be preferred to surgical resection.

Previously, surgery was the therapeutic option of choice for localized, extra-abdominal, small volume desmoid tumors. However, surgery is no longer regarded as the cornerstone of desmoid tumor treatment given the high rate of relapse after surgery, which exceeds 60% in larger studies, and the frequent observation of spontaneous disease regression and stabilization (Penel, 2017). Variables associated with local recurrence post-surgery include tumor location, age of the participant, and quality of the surgical resection (Kasper, 2011).

Radiotherapy has been used both in the adjuvant setting after surgery and in the primary setting, mainly for extra-abdominal tumors (Kasper, 2011). Radiotherapy after surgery is an independent positive prognostic factor for local recurrence and overall survival, and radiotherapy alone or in combination with surgery led to significantly lower recurrence rates (Kasper, 2011).

Modalities studied in clinical studies include hormonal therapy since virtually all desmoid tumors express nuclear estrogen receptor-β, albeit at low receptor levels (Janinis, 2003); and nonsteroidal anti-inflammatory drugs, such as indomethacin and sulindac; however, limited responses have been observed with these agents.

In the case of unresectable, rapidly growing and/or symptomatic and/or life-threatening desmoid tumors, traditional chemotherapy may be considered. Kasper et al. (2011), provided an overview of chemotherapy regimens that have been studied in participants with advanced disease

For patients with relapsed or recurrent desmoid tumors, or for patients with desmoid tumors that are not amenable to surgery or radiotherapy, or if surgery is potentially mutilating, various systemic therapy have been studied, although little in controlled clinical studies. Schöffski et al conducted a survey of physician's preference for systemic treatment for patients with advanced desmoid tumors using a structured questionnaire (Schöffski, 2018). Results indicated that disease progression and failure of local therapy were typical indications for the use systemic therapy. Thus, clinical studies with systemic agents should ideally select a homogenous population with advanced, progressive, and symptomatic desmoid tumors and/or functional impairment after failure of observation only strategies and/or local treatments such as surgery or radiotherapy.

Due to the spontaneous regression observed in participants with desmoid tumors, studies should ideally be randomized, with physician's choice or placebo as potential comparators.

Meaningful responses have been observed with tyrosine kinase inhibitors, such as imatinib (Kasper, 2017) and sorafenib. Recently, the results from a Phase 3 study of sorafenib compared to placebo were published in The New England Journal of Medicine (Gounder, 2018). The study enrolled 87 participants with progressive, symptomatic or recurrent desmoid tumors that were randomized 2:1 to sorafenib (n=50) or placebo (n=37). The median PFS for placebo was 11.3 months (95% CI [5.7, not evaluable]) and was not reached for sorafenib (HR = 0.13, 95% CI [0.05, 0.31], $p < 0.001$). The objective response rate (ORR) for sorafenib was 33% (95% CI, 20 to 48) and for placebo was 20%, (95%CI, 8 to 37). Spontaneous regressions are known to occur in desmoid patients. This study confirmed the need for a control group (Schöffski, 2018) in desmoid tumor clinical studies particularly given the spontaneous response rate in the placebo group.

Additional targeted agents such as sirolimus and pazopanib are also being studied in participants with desmoid tumors (NCT01265030 and NCT01876082, respectively).

2.2.3.1. Clinical Studies with Nirogacestat

2.2.3.1.1. Study A8641014A: Phase 1 study of PF-03084014 in participants with advanced solid tumor malignancy and T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma

Messersmith and colleagues conducted a Phase 1, dose-finding study to determine the maximum tolerated dose (MTD), the recommended Phase 2 dose (RP2D), and to evaluate safety of continuous administration of nirogacestat in participants with advanced solid tumors (Messersmith, 2015). Sixty-four participants received doses of nirogacestat and the MTD was determined to be 220 mg, administered twice daily (BID). The RP2D was determined to be 150 mg BID, given comparable NOTCH related target inhibition. The most common reason for discontinuation from nirogacestat was objective progression or relapse of disease (32 participants). The most common primary diagnosis was desmoid tumor (9 participants), with a mean duration since diagnosis of 7.7 years. All participants received surgeries and about half of the participants received radiation therapy. The majority (60 [93.8%] participants) received previous systemic therapies and more than half (35 [54.7%] participants) had systemic therapies for > 3 regimens.

Of the 64 participants with solid tumors, 62 experienced at least 1 adverse event (AE), and 54 experienced at least 1 treatment-related AE (1 participant with a Grade 1 AE of upper respiratory infection was excluded from the analysis due to a database error). The most common treatment-related AEs were diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite. The majority of these AEs were Grade 1 to Grade 3. Dose reductions due to treatment-related AEs were infrequent and were reported in 9 (14%) participants at various times during treatment (from Cycle 1 to Cycle 10). Across dose levels, 5 (7.8%) participants had Grade 2 or Grade 3 diarrhea that resolved with dose reduction. Temporary discontinuation occurred in 21 (32.8%) participants, 13 (20.3%) of which were for a treatment-related AE. All treatment-related AEs that led to temporary discontinuation (diarrhea, hypophosphatemia, rash, nausea, vomiting, and fatigue) or dose

reduction were Grade 1 to Grade 3, and most resolved following temporary discontinuation or dose reduction. Seven (10.9%) participants permanently discontinued treatment primarily owing to an AE; of these, 4 (6.3%) participants discontinued for a treatment-related AE: one each for Grade 4 anaphylactic shock (100 mg BID) (an event thought to be related to co-administration of IV morphine), Grade 1 visual impairment (150 mg BID), Grade 3 drug hypersensitivity (220 mg BID), and Grade 3 rash (330 mg BID). The hypersensitivity reaction (rash associated with chest tightening and shortness of breath) resolved with intravenous steroid therapy after discontinuation of study treatment.

There were 46 participants with solid tumors evaluable for response. Overall, ORR was 13.0% (95% CI [94.9, 26.3]) for these participants. Six participants had an ORR with 1 complete response (CR) (participant with thyroid cancer) and 5 partial responses (PRs). All 5 PRs were reported by participants with desmoid tumors, who accounted for 71.4% (95% CI [29.0, 96.3]) of the 7 participants with desmoid tumors evaluable for response. At the time of data cutoff, all 6 responders were censored in the calculation of duration of response. All 5 responders with desmoid tumors had not progressed and were censored at the time of data cutoff, with 4 still on study and 1 discontinued due to noncompliance. The participant with thyroid cancer with CR later had recurrence of disease but was censored at the last disease assessment of CR due to missed tumor assessments.

Overall, nirogacestat was well tolerated with an MTD determined to be 220 mg BID and a RP2D to be 150 mg BID. The best tumor responses were 5 PRs out of 7 evaluable participants with desmoid tumors.

Villalobos and colleagues reported the long-term follow-up of the 7 participants with desmoid tumors from the Phase 1 study (Villalobos, 2018). As previously described, 5 of the 7 participants with desmoid tumors had a PR with a mean time to response of 11.9 months. All participants that achieved a PR continued to maintain response between 48 and 73+ months. Four participants who discontinued therapy remained free of progression between 11 and 53+ months. One participant had a PFS of > 42 months, with a 17% decrease in the target lesion. Prolonged disease control was observed for 6 out of 7 of the participants with desmoid tumors treated with nirogacestat.

2.2.3.1.2. National Cancer Institute Protocol 14-C-0007: Phase 2 study of gamma secretase inhibitor PF-03084014 in adults with desmoid tumors/aggressive fibromatosis (NCT01981551)

A Phase 2 study was conducted by investigators at the National Cancer Institute (NCI) to evaluate the ORR after therapy with nirogacestat in participants with recurrent, refractory, progressive desmoid tumors (Kummar, 2017). Seventeen participants received daily doses of nirogacestat at 150 mg BID continuously in 3-week cycles. Response to treatment was evaluated at Cycle 1 and every 6 cycles (18 weeks) thereafter by Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1. Of the 17 participants treated in the study, 15 had mutations in APC or CTNNB1 genes. Sixteen participants were evaluable for response; 5 participants experienced a confirmed PR and had been on study for more than 2 years, and the remaining 11 participants had stable disease. No participant progressed on

study. The AE profile was consistent with previous reports (Messersmith, 2015) and consisted of all participants experiencing at least 1 Grade 1 or Grade 2 AE; and the most commonly reported AEs were diarrhea and skin disorders. Four participants had a dose reduction while on study. Two participants received a reduced dose of 100 mg BID as a result of persistent Grade 3 nausea and diarrhea, 1 participant developed urticaria nonresponsive to dose reduction and came off study, and 1 participant developed a Grade 2 maculopapular rash, which resolved with dose reduction. The only Grade 3 AE attributable to study treatment was hypophosphatemia, reported in 8 participants, and is a known class effect of GS inhibitors.

2.3. Rationale for Nirogacestat in Desmoid Tumors

Emerging evidence in recent years presents the Notch pathway as a promising target for treatment of solid tumors. It has been reported that aberrant Notch activation and deregulated expression of Notch ligands and targets are associated with a broad panel of solid tumors. At least 3 Notch members (NOTCH1, NOTCH3, and NOTCH4) have been found to be involved in solid tumors.

The molecular mechanism for the oncogenic activity of Notch intracellular domain (NICD) may include inhibiting differentiation, promoting survival, or accelerating proliferation. Potential oncogenic targets of NOTCH1 include Myc, cyclin D1, and several other factors. In the case of Myc, evidence demonstrates that Myc is a direct target gene of NOTCH1 and essential for development of both T-cell leukemia and mammary tumors in mice (Sharma, 2006; Klinakis, 2006).

Recent studies suggest crosstalk between the Wnt and Notch pathways (Rodilla, 2009; Rampazzo, 2013). It has been shown that Notch activity is increased in colorectal cancer cells through upregulation of JAG1 mediated by β-catenin, and levels of hairy and enhancer of split-1 (Hes1) messenger ribonucleic acid are significantly upregulated in APCmin/+ mouse intestinal cancer models (Ungerback, 2011). Expression of NOTCH1 and Hes1 have been observed in mesenchymal stromal cells found in desmoid tumor, suggesting that the Notch pathway is possibly related to desmoid tumorigenesis (Shang, 2015). Importantly, nirogacestat has been shown to inhibit the Notch pathway in desmoid tumors by inhibiting NICD and Hes1 expression and this blockade results in grow arrest rather than apoptotic cell death in desmoid tumors (Shang, 2015).

This collective data suggests that Notch signaling plays an important role in cancer development. Hence, inhibition of Notch signaling is an important strategy for therapeutic treatment.

2.4. Rationale for Participant Population and Placebo Arm

Desmoid tumors most commonly occur in individuals between the ages of 15 to 60 years, more often in young adults, with the peak age of about 30 years, and a 2- to 3-fold predominance in females (de Camargo, 2010; Skubitz, 2017). This Phase 3 study will enroll participants ≥ 18 years old. The pharmacokinetics (PK) and optimal dosing of nirogacestat in younger participants has not been established. A future study in pediatric participants is planned.

There is no FDA-approved therapeutic option for the treatment of desmoid tumors, nor is there an accepted standard of care for patients with advanced progressing tumors. The population will be assessed by a wait-and-see approach and depending on the tumor growth and location, different therapeutic options may be considered. The recently analyzed Phase 3 study of sorafenib versus placebo (Gounder, 2018) showed a significant improvement in PFS in the sorafenib arm, but also demonstrated objective responses in the placebo group highlighting the need for this control in Phase 3 studies.

2.5. Benefit/Risk Assessment

To date, the safety profile of single-agent nirogacestat in participants with advanced cancer has been characterized by manageable and reversible toxicities. The most frequently reported AEs were diarrhea, fatigue, nausea, vomiting, hypophosphatemia, cough, and rash. The majority of the events were mild-to-moderate in intensity. Additionally, a Phase 2 (investigator-initiated) study in adult participants with desmoid tumors showed a similar AE profile (Kummar, 2017). All participants in the study experienced at least one Grade 1 or Grade 2 AE; with the most commonly reported events being diarrhea and skin disorders.

Based on the mechanism of action and nonclinical/clinical study data, the important identified risks associated with nirogacestat administration include notch-related effects on reproductive function and fertility, notch-related effects on hematopoietic (immune) function, notch-related effects on gastrointestinal function, skin rash, and hypophosphatemia. Important potential risks include effects on the hepatic system, including potential liver cholestasis. These risks will be assessed by routine pharmacovigilance measures.

Additionally, measures are in place to minimize potential risks to study participants, and review of safety data will be conducted on an ongoing basis in order to identify new safety signals that may arise during the program.

The results of the nonclinical toxicology and safety pharmacology studies, together with the clinical experience in participants with advanced cancers (Sections 2.2.3.1.1 and 2.2.3.1.2), support the hypothesis that nirogacestat may represent an important therapeutic approach in patients with desmoid tumors. Thus, the projected benefit/risk balance is considered favorable for further development in this patient population.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirogacestat may be found in the Investigator's Brochure.

The study will utilize an independent data monitoring committee (DMC) and will operate according to an established Charter (Section 9.5.1). In addition, a protocol steering committee was established to support the development of nirogacestat for the treatment of desmoid tumor/aggressive fibromatosis. The purpose and provisions of the DMC will be specified in the DMC Charter.

3. OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
To determine the efficacy (as defined by PFS) of nirogacestat in adult participants with progressing DT/AF.	PFS defined as the time from randomization until the date of assessment of progression or death by any cause. Progression will be determined radiographically using RECIST v1.1 (Eisenhauer, 2009; Section 10.8) or clinically as assessed by the investigator. Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.
Secondary	**Secondary**
To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of AEs;	Safety endpoints will include incidence of treatment-emergent AEs, changes in laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs). Tolerability will be assessed according to toxicities graded by NCI Common Terminology Criteria for Adverse Events v5.0;
To determine the overall response rate (CR + PR) of nirogacestat in participants with progressing DT/AF;	Overall response rate, defined as the proportion of participants with CR + PR assessed by central reader using RECIST v1.1 Criteria;
To determine the duration of response;	Duration of response for participants whose best response is CR or PR;
To compare tumor volume changes measured by MRI in participants with progressing DT/AF; and	Change in tumor volume from baseline as assessed by MRI volumetric; and
To evaluate desmoid tumor symptoms and impacts using patient-reported outcomes (PROs).	Symptoms and impacts will be assessed by evaluating change from baseline on the following PROs:

	• GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS); • Brief Pain Inventory short form; • Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks; and • European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30.
Exploratory	**Exploratory**
To evaluate desmoid tumor symptoms and impacts using PROs;	Symptoms and impacts will be assessed by evaluating changes using the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC);
To perform genotyping for germline and somatic mutation in APC and CTNNB1 genes;	Assess the frequency and distribution of each mutation;
To assess modulation of the Notch pathway by evaluating NOTCH response genes in tumor biopsies at screening and disease progression or end of treatment (EOT);	Change in expression pre- and post-dose on Notch pathway genes;
To assess MRI T2 hyperintensity at baseline and post-drug administration;	Assess the percent change in MRI T2 intensity;
To inform development of a population PK model of nirogacestat; and	To optimally collect sparse PK samples to increase precision of model parameters; and
To perform exposure-response analysis using a final population PK/PD (PopPK/PD) model.	To determine the relationship between exposure and primary, secondary, and/or exploratory efficacy and safety endpoints.
To evaluate the effect of nirogacestat on clinical events related to disease specific desmoid tumor co-morbidity.	Summarize the incidence and frequency of events which may include hospitalization due to small bowel obstruction, hospitalization due to desmoid tumor-related pain, surgery for desmoid tumor.

4. STUDY DESIGN

4.1. Overall Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. Approximately 118 eligible participants will be randomized to study treatment (nirogacestat or placebo) in a 1:1 ratio. Randomization will be stratified by primary tumor location (intra-abdominal or extra-abdominal [Section 6.3.1]).

This study will consist of 2 phases: the double-blind phase and the optional open-label extension (OLE) phase. Refer to the schedule of activities (SoA; Sections 1.3.1 and 1.3.2) for details on assessments and timing of study visits.

Refer to Section 1.2 for the study schema.

4.1.1. Overall Design for the Double-Blind Phase:

Participants will be screened up to 28 days prior to the first dose of study treatment and eligibility will be based on inclusion and exclusion criteria (Sections 5.1 and 5.2). Participants will be randomized to study treatment at Cycle 1 Day 1 using interactive response technology (IRT), and will orally administer 150 mg BID, continuously in 28-day cycles.

Following the baseline visit (Cycle 1 Day 1), participants will return to the clinic for study visits at Cycle 1 (Days 8, 15, 22), Cycle 2 (Day 28), Cycle 4 (Day 1) and then on Day 1 of every 3 cycles thereafter.

Participants will remain in the double-blind phase until:

- Participant experiences death;
- Central Imaging Review determines that the participant has radiographic progressive disease (using RECIST v1.1);[1]
- The investigator determines the participant is experiencing clinical progression which is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF; [2]
- Participant prematurely discontinues study treatment for any reason;
- The study is stopped by the sponsor for any reason; or
- The required number of PFS events have been observed and the primary PFS analysis has been completed (based on current statistical assumptions, this is anticipated to be approximately 2 years after the first participant is randomized).[3]

[1]If Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will return to the site for an end of treatment (EOT) visit within 14 days of the notification from the

central imaging core laboratory. During the EOT visit, the participant will be unblinded and have the option to enter the OLE phase if eligible (Section 6.7.1).

[2]If a participant has clinical progression as determined by the investigator; the participant will return to the site for an end of treatment (EOT) visit within 14 days of the date of clinical progression. During the EOT visit, the participant will NOT be unblinded; and will NOT be eligible to enter the optional OLE phase.

[3]When the required number of PFS events have been observed and the primary PFS analysis has been completed, all remaining participants in the double-blind phase will be unblinded. And if eligible, they will have the option to enter the OLE phase.

4.1.2. Overall Design for the Optional OLE Phase:

Only eligible participants may enroll in the OLE phase of the study. Refer to Sections 6.7.2 and 6.7.3 for the OLE phase eligibility criteria.

The Cycle 1 Day 1 visit of the OLE phase should be conducted on the same day as, or within 24 hours after, the double-blind EOT visit. A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1.

Participants will be enrolled in the OLE phase using the IRT only after (1) all ongoing AEs/SAEs from the double-blind phase have been assessed for causality in a blinded manner by the investigator or qualified designee, and (2) all AE/SAE causality assessments have been entered into the electronic case report form (eCRF). In addition, all double-blind EOT visit assessments must be completed prior to unblinding and administering the first dose of open-label study treatment. Refer to Section 6.3.2.1 for more detail on the required unblinding criteria.

Participants who were randomized to receive placebo in the double-blind phase will receive their first dose of study treatment at the site followed by a 3-hour observation period.

Participants who were randomized to nirogacestat in the double-blind phase may take their first dose of open-label study treatment at home (observation period is not required).

Following the OLE baseline visit (Cycle 1 Day 1), participants who were previously randomized to receive placebo in the double-blind phase will return to the clinic for study visits at Cycle 1 (Day 8, 15, 22) and Cycle 2 (Day 28). Participants who were previously randomized to nirogacestat in the double-blind phase will not return to the clinic until the Cycle 4 Day 1 visit.

All participants will have study visits at Cycle 4 Day 1 and then on Day 1 of every 3 cycles thereafter.

Participants will remain in the OLE phase until:

- Participant experiences death;
- Central Imaging Review determines that the participant has radiographic progressive disease (using RECIST v1.1);
- The investigator determines the participant to have clinical progression which is defined as the onset or worsening of symptoms resulting in a global deterioration of health status

causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF;

- Participant prematurely discontinues study treatment for any reason;
- The study is stopped by the sponsor for any reason;
- Participant qualifies for sponsor's Continued Access Plan; or
- Nirogacestat is commercially available.

4.2. Scientific Rationale for Study Design

Based on the promising, prolonged tumor responses and overall tolerability with nirogacestat observed in the Phase 1 and Phase 2 studies, this Phase 3 double-blind, placebo-controlled study is being proposed to determine the efficacy and safety in participants with unresectable, recurrent or relapsed progressing desmoid tumors. Progression-free survival was selected as the primary endpoint based on the previous clinical studies with nirogacestat in desmoid participants with progressing tumors and the observation that only one participant progressed after 15 months on therapy (1 out of 24 participants) (Villalobos, 2018 and Kummar, 2017). The rate of progression in untreated desmoid patients is about 11 months (Gounder, 2018). A placebo group was chosen because of the known spontaneous regressions that can occur with desmoid tumors. Progressing desmoid tumors can be unrelenting to patients particularly when they are unresectable or unresponsive to systemic treatment and halting progression, particularly when paired with tumor shrinkage, is a significant outcome for patients. Because of the size and location of desmoid tumors they can often be associated with pain, loss of range of motion, and impact on daily living. This study incorporates outcome tools to assess change from baseline in these outcome measures, as changes in pain, for example, have been observed in participants treated with nirogacestat that had significant tumor shrinkage (Kummar, 2017).

Given the unique characteristics of DT/AF, applying RECIST v1.1 alone is not always an adequate means of capturing the entirety of the disease progression and its clinical impact on participants. In particular, DT/AF tumors have been shown to grow in an asymmetric nature that can infiltrate multiple layers of fascia, neurovascular bundles and complex joint spaces (Gounder, 2017; Villalobos, 2017). This asymmetric growth also impacts the plane in which RECIST v1.1 measurements are performed such that the plane selected for review at the beginning of the study may not match the plane which ultimately shows progressive disease. To address the complexities of evaluating DT/AF lesions, progression will be determined both radiographically using Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1 (Eisenhauer, 2009; Section 10.8) and clinically as assessed by the investigator.

4.3. Justification for Dose

An open-label, non-randomized, Phase I dose finding study (Messersmith, 2015) in participants with advanced solid tumors was conducted to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for future clinical development of nirogacestat. In the dose-

finding portion of the study, the MTD of nirogacestat administered BID continuously for 21 days was established at 220 mg BID in participants with advanced solid tumors. Additional participants were subsequently enrolled in the expansion cohort at 150 mg or 220 mg BID. The RP2D in participants with advanced solid tumors was determined to be 150 mg BID by comparing the tolerability, PK, and pharmacodynamic profile of nirogacestat at these 2 doses. At a dose level of 150 mg BID, the most frequently reported AEs were diarrhea (70%), fatigue (44%), nausea (39%), decreased appetite (26%), vomiting (26%), and hypophosphatemia (22%). Analysis of whole blood samples demonstrated that HES4 showed the most consistent PD response, with a greater than 2-fold down-modulation observed in 17 of 19 evaluable participants with solid tumors. Additionally, in participants with advanced desmoid tumors, there appeared to be a clear response to nirogacestat treatment. Nirogacestat was also investigated as a single agent in a Phase 2 study in 19 participants with triple-negative breast cancer at the RP2D of 150 mg BID. Neither efficacy nor PK were summarized for this study, but the AE profile was consistent with the Phase 1 study. Lastly and importantly, nirogacestat at 150 mg BID was studied in another Phase 2 study conducted by the NCI in participants with progressing desmoid tumors (Kummar, 2017). In this study, nirogacestat activity was established with 5 PR (29%) out of 16 evaluable participants. The dose of 150 mg BID was chosen for this Phase 3 clinical study based on the safety profile at this dose as well as the encouraging tumor responses in participants with desmoid tumors.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3) (including telephone contact) for the last participant in the study globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

The inclusion criteria apply to the double-blind phase of the study only. The inclusion criteria for the OLE phase can be found in Section 6.7.2.

Participants are eligible to be included in the double-blind phase only if all the following criteria apply:

Age

1. Participant must be at least 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participant has histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan.
3. Participant has:
    a. Treatment naïve, measurably progressing DT/AF that is deemed not amenable to surgery without the risk of significant morbidity;

       OR

    b. Recurrent, measurably progressing DT/AF following at least one line of therapy;

       OR

    c. Refractory, measurably progressing DT/AF following at least one line of therapy.
4. Participant has a DT/AF tumor where continued progressive disease will not result in immediate significant risk to the participant.
5. Participant agrees to provide archival or new tumor tissue for re-confirmation of disease.
6. If participant is currently being treated with **any** therapy for the treatment of DT/AF, this must be completed at least 28 days (or 5 half-lives, whichever is longer) prior to first dose of study treatment. All toxicities from prior therapy must be resolved to ≤ Grade 1 or clinical baseline.
7. Participants who are receiving chronic nonsteroidal anti-inflammatory drugs (NSAIDs) as treatment for conditions **other than** DT/AF must be receiving them prior to the documented DT/AF progressive disease (inclusion criteria 2) and on a stable dose for at least 28 days prior to first dose of study treatment.

8. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at screening (refer to Section 10.7 for ECOG performance status scale).
9. Participant has adequate organ and bone marrow function as defined by the following screening laboratory values:
    a. Absolute neutrophil count ≥ 1500 cells/µL;
    b. Platelets ≥ 100,000µL;
    c. Hemoglobin ≥ 9 g/dL;
    d. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (isolated bilirubin > 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%);
    e. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase) ≤ 2 × ULN; and
    f. Serum creatinine ≤ 1.5 × ULN or if creatinine > 1.5 × ULN then calculated creatinine clearance must be ≥ 60 mL/min (using the Cockcroft-Gault formula);
10. Participant can swallow tablets and has no gastrointestinal conditions affecting absorption.

Sex

11. Male or Female

    Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    a. **Male participants:**
    Male participants are eligible to participate if they agree to the following during the treatment period and for at least 90 days after the last dose of study treatment:

    - Refrain from donating or preserving sperm;

      PLUS either**:**

    - Be abstinent from sexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent;

      OR

    - Must agree to use a male condom when having sexual intercourse with women of childbearing potential (WOCBP). An additional form of contraception as described in Section 10.4 should also be used by the female partner, if she is of childbearing potential. Refer to Section 10.4 for definition of WOCBP.

    b. **Female participants:**
    A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    - Is not of childbearing potential (not WOCBP).

OR

- Is of childbearing potential but is abstinent or using 1 highly effective contraceptive method, as described in Section 10.4 during the treatment period and until 6 months after the last dose of active study treatment. A second method of contraception is required if the participant is using hormonal contraception, as coadministration with nirogacestat may alter the plasma concentrations of hormonal contraceptives resulting in reduced efficacy. Additionally, the participant agrees not to harvest or donate eggs (ova, oocytes) for the purpose of reproduction during the treatment period and for at least 6 months after the last dose of active study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at the baseline visit prior to the first dose of study treatment.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

12. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

These criteria only apply to the double-blind phase of the study. The exclusion criteria for the OLE phase can be found in Section 6.7.3.

Participants are excluded from the double-blind phase if any of the following criteria apply:

Medical Conditions

1. Participant has known malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of nirogacestat (e.g., gastric bypass, lap band, or other gastric procedures that would alter absorption); delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.
2. Participant has experienced any of the following within 6 months of signing informed consent:
    - clinically significant cardiac disease (New York Heart Association Class III or IV);
    - myocardial infarction;
    - severe/unstable angina;

- coronary/peripheral artery bypass graft;
- symptomatic congestive heart failure;
- cerebrovascular accident;
- transient ischemic attack; or
- symptomatic pulmonary embolism.

3. Participant has abnormal QT interval corrected by Fridericia's formula (> 450 msec for male participants, > 470 msec for female participants, or > 480 msec for participants with bundle branch block) after electrolytes have been corrected (triplicate ECG readings, done approximately 2-3 minutes apart and averaged) at screening.
4. Participant is using concomitant medications that are known to prolong the QT/QTcF interval including Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) antiarrhythmics at the time of informed consent. Non-antiarrhythmic medications which may prolong the QT/QTcF interval are allowed provided the participant does not have additional risk factors for Torsades de Pointes (TdP).
5. Participant has congenital long QT syndrome.
6. Participant has a history of additional risk factors for Torsades de Pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
7. Participant has had lymphoma, leukemia, or any malignancy within the past 5 years at the time of informed consent, **except** for any locally recurring cancer that has been treated curatively (e.g., resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast), with no evidence of metastatic disease for 3 years at the time of informed consent.
8. Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones).

Prior/Concomitant Therapy

9. Participant previously received or is currently receiving therapy with GS inhibitors or anti-Notch antibody therapy.
10. Participant is currently using any treatment for DT/AF including tyrosine kinase inhibitors (TKIs), NSAIDs (chronic daily use – except as in inclusion criterion 7) or any investigational treatment 28 days (or 5 half-lives, whichever is longer) prior to the first dose of study treatment.

    OR

    Participant has started any treatment for DT/AF after the documented DT/AF progressive disease (inclusion criteria 2).

11. Participant is currently using or anticipates using food or drugs that are known strong/moderate cytochrome P450 3A4 (CYP3A4) inhibitors, or strong CYP3A inducers within 14 days prior to the first dose of study treatment.

Prior/Concurrent Clinical Study Experience

12. Participant is currently enrolled or was enrolled within 28 days of first dose of study treatment in another clinical study with any investigational drug or device. Participation in observational studies may be permitted with prior approval from the medical monitor/sponsor.

Diagnostic assessments

13. Participant has a positive human immunodeficiency virus antibody test.
14. Participant has presence of Hepatitis B surface antigen at screening.
15. Participant has a positive Hepatitis C antibody or Hepatitis C ribonucleic acid (RNA) test result at screening or within 3 months prior to starting study treatment.

    NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

    Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

Other Exclusions

16. Participant is unable to tolerate MRI or for whom MRI is contraindicated.
17. Participant with active or chronic infection at the time of informed consent and during the screening period.
18. Participant has experienced other severe acute or chronic medical or psychiatric conditions, including recent (within 1 year of signing informed consent) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.
19. Participant has known hypersensitivity to the active substance or to any of the excipients of nirogacestat or placebo (Table 2).
20. Participant is unable to comply with study related procedures (including, but not limited to, the completion of electronic patient report outcomes (ePROs), or the ePRO questionnaires are not available in the participant's preferred language)

5.3. Lifestyle Considerations

1. No specific lifestyle restrictions are required in this study.
2. Study treatment may be taken without regard to food.

3. Refer to Section 6.5 for more detail on concomitant therapy including exclusions and restrictions.

5.3.1. Meals and Dietary Restrictions

Participants must refrain from consuming Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, or grapefruit hybrids at least 14 days prior to the first dose of study treatment and throughout the double-blind and open-label phase.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment (nirogacestat or placebo). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened at any time if provided the participant has **not** screen failed on any of the following exclusion criteria: #1, 5, 6, 8, 9, 13, or 19.

Participants do not need to wait the full 28 days of the screening period to rescreen. There is no set limit to how many times a participant may be rescreened if the investigator considers the rescreening medically and scientifically appropriate, and the screening assessments continue to be tolerable for the participant. Rescreened participants must be re-consented and will be assigned a new participant number at the time of rescreening, which can be found on a new screening laboratory requisition form and will need to be entered into the IRT.

6. STUDY TREATMENT

Study treatment for this study is investigational (nirogacestat or placebo) and intended to be administered to a study participant according to the study protocol.

6.1. Study Treatment Administered

- Participants will be instructed to swallow tablets whole and not to chew them prior to swallowing.
- No tablet should be ingested if it is broken, cracked, or otherwise compromised (e.g., not fully intact).
- Participants should take their dose BID orally, approximately every 12 hours, without regard to food.
- Participants will be instructed to record their daily administration of each study treatment dose in an eDiary using a home electronic patient report outcome (ePRO) device, which will be provided by the sponsor.
- If a participant misses a scheduled dose of study treatment, and it is within 6 hours of the scheduled dose, the participant should immediately administer the missed dose and resume study treatment in accordance with the normal administration schedule. If more than 6 hours have elapsed since the time of scheduled administration, the participant should be instructed not to administer the missed dose and to resume study treatment as prescribed.
- Participants should not take 2 doses together to “make up” for a missed dose.
- If a participant vomits any time after taking a dose, then they must be instructed not to take another dose to “make up” for vomiting, but rather to resume subsequent doses as prescribed.
- If a participant inadvertently takes 1 extra dose, then the participant should not take the next scheduled dose of study treatment.
- Delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.

Table 2 Study Treatments Administration

ARM Name	Experimental	Control
Treatment Name	Nirogacestat	Placebo
Type	Drug	Drug
Dose Formulation	Tablet[1]	Tablet
Unit Dose Strength(s)	50 mg	50 mg
Dosage Level(s)	150 mg BID	150 mg BID
Route of Administration	Oral	Oral
Sourcing	Sponsor will provide sites with study treatment for individual participant distribution	Sponsor will provide sites with study treatment for individual participant distribution
Packaging and Labeling	Study treatment will be provided in 90 count bottles. Each bottle will be labeled as required per country requirement	Study treatment will be provided in 90 count bottles. Each bottle will be labeled as required per country requirement
Former Name	PF-03084014	Not Applicable
Ingredients	Uncoated Tablets: PF-03084014-04; Microcrystalline Cellulose; Lactose Monohydrate; Sodium Starch Glycolate; and Magnesium Stearate. Opadry® QX Film Coated Tablets: Macrogol (PEG) Polyvinyl Alcohol Graft Copolymer, Talc, Titanium Dioxide, GMCC Type 1,	Microcrystalline Cellulose; Lactose Monohydrate; Sodium Starch Glycolate; and Magnesium Stearate.

	Polyvinyl Alcohol – Part Hydrolyzed, Yellow #6 / Sunset Yellow FCF Aluminum Lake, Iron Oxide Yellow	

[1] Nirogacestat tablets may be uncoated or coated with a non-functional aqueous film coat (Opadry® QX) in the OLE phase of the study. In the double-blinded phase of the study, nirogacestat will only be dispensed in an uncoated tablet.

6.1.1. Double-Blind Phase Dosing Administration

The first dose of double-blind study treatment (3 × 50 mg tablets) will be administered at the site on Cycle 1 Day 1 followed by a 3-hour observation period. To minimize time required onsite, the observation period may be shortened to 2 hours temporarily during a public health emergency (e.g., COVID-19) with prior medical monitor / sponsor approval.

Throughout the double-blind phase, participants will administer 150 mg (3 × 50 mg nirogacestat tablets or placebo) of study treatment BID (approximately every 12 hours, without regard to food), continuously in 28-day cycles.

6.1.2. Open-Label Phase Dosing Administration

Participants who were randomized to receive placebo in the double-blind phase will receive their first dose of open-label study treatment at the site followed by a 3-hour observation period.

Participants who were randomized to nirogacestat in the double-blind phase may take their first dose of open-label study treatment at home. An observation period at the site is not required.

Throughout the OLE phase, participants will administer 150 mg (3 × 50 mg tablets) of study treatment BID (approximately every 12 hours, without regard to food), continuously in 28-day cycles. To minimize time required onsite, the observation period may be shortened to 2 hours temporarily during a public health emergency (e.g., COVID-19) with prior medical monitor / sponsor approval.

6.1.3. Study Treatment Errors

Study treatment errors may result from the administration or consumption of the wrong study treatment, by the wrong participant, at the wrong time, or at the wrong dosage strength. Such study treatment errors are to be captured on the AE page of the eCRF and on the SAE form when appropriate. In the event of a dosing error, the medical monitor/sponsor should be notified immediately.

Study treatment errors are reportable irrespective of the presence of an associated AE/SAE, including errors involving participant exposure to the product.

Missed doses are not considered dosing errors.

6.2. Preparation/Handling/Storage/Accountability

- Study treatment will be dispensed to participants every 3 cycles during scheduled study visits as described in the SoA (Section 1.3) or unscheduled visits if study treatment is damaged/lost or a dose modification (Section 6.6) is necessary.
- Participants will be instructed to keep their study treatment in the bottles provided and not transfer it to any other containers.
- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment shipments received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants randomized in the IRT may receive study treatment and only authorized site staff may supply study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Study treatment should be dispensed at the study site; however, direct to participant (DTP) shipping may be allowed with advance approval from the Sponsor in the event of a public health crisis such as COVID-19. Direct to participant shipping is not allowed at the C1D1 visit in the double blind or OLE phase of the study.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Study treatment returned by the participant will not be re-dispensed.
- Further guidance and information about the handling, storage, and final disposition of unused study treatment (bottles/tablets) are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

- Prior to participants being randomized to study treatment, the following activities must be completed:
    1. Participant must sign the ICF (Section 10.1.3) and complete all screening assessments (Section 1.3.1).
    2. Site must submit the Pre-Randomization RECIST v1.1 Calculation Worksheet at least 7 days prior to Cycle 1 Day 1 (Section 8.1.1.1).
    3. Site must submit the screening visit scan(s) to the central imaging core laboratory as early in the screening period as possible to confirm scan quality (Section 8.1.1).
    4. Site must confirm that the participant meets all study entry criteria (Sections 5.1 and 5.2).

5. Participant must complete all pre-randomization baseline visit assessments. Refer to Section 1.3.1 and Baseline and Cycle 1 Day 1 (double-blind phase) for additional details.

- At Cycle 1 Day 1, once all of the above activities have been completed, participants will be centrally assigned to randomized study treatment (nirogacestat or placebo) using the IRT. Before the study is initiated at a site, instructions and log-in information for the IRT will be provided to appropriate site personnel.
- Randomization will be stratified based on the following tumor locations:

  1. Intra-abdominal (including mesentery and pelvis);

     OR

  2. Extra-abdominal (including head/neck, para-spinal, extremities, abdominal wall, chest wall, and other locations).

  If the participant has multiple target tumors that are located both in the intra- and extra-abdominal location, the tumor should be classified as intra-abdominal.

- The tumor location used for stratification should be the same as the reported target lesion(s) used for assessment of the primary endpoint. The location of the target tumor(s) will be selected by the investigators as the basis for inclusion in the study and will be documented on the Pre-Randomization RECIST v1.1 Calculation Worksheet (Section 8.1.1.1).

6.3.2. Blinding

For the double-blind phase, the participant, investigator, and all other clinical site personnel will be blinded to the assigned treatment allocation. All sponsor personnel will also be blinded except for the sponsor's quality assurance designee(s), safety designee(s), and clinical supply material designee(s).

If Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will then return for the EOT visit which will be conducted in a completely blinded fashion. All EOT assessments and all ongoing AEs/SAEs must (1) be assessed for causality by the investigator or qualified designee in a blinded manner and (2) recorded in the eCRF prior to the unblinding of the study treatment allocation (Section 6.3.2.1).

Study participants who discontinue due to clinical progression will NOT be unblinded and will NOT be eligible to enroll into the optional OLE phase of the study. These participants should be discontinued from the study after completing an EOT and FUP visit as specified in applicable SoA table.

If a participant discontinues study treatment for any reason other than radiographic progressive disease as determined via central review, the study treatment allocation will not be unblinded.

6.3.2.1. Breaking the Blind

Sites will be provided instructions on how to break the blind in the IRT prior to study initiation.

The study treatment blind is **not** to be broken unless one of the following criteria apply (unblinding at the clinical site for any other reason will be considered a protocol deviation and the unblinded participant will be permanently discontinued from the study):

1. Emergency situations:
    - In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted.
    - Participant safety must always be the first consideration in making such a determination.
    - If the investigator decides that unblinding is warranted, the investigator will make every effort to contact the medical monitor/sponsor prior to unblinding a participant's study treatment assignment unless this could delay emergency treatment of the participant. Refer to Section 10.10.3 for the medical monitor contact information.
    - The sponsor or medical monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.
    - If the blind is broken for emergency reasons, the unblinded participant will be permanently discontinued from the study and it not eligible to enter the OLE phase.
2. Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1);
    - Prior to unblinding in this situation, the following criteria must be met:
        - All double-blind EOT study assessments have been completed in a blinded manner (refer to SoA table Section 1.3.1 for complete list of assessments).
        - All ongoing AEs/SAEs from the double-blind phase have been assessed for causality by the investigator or qualified designee in a blinded manner and recorded in the eCRF.
        - Sponsor designee has confirmed that the criteria above have been met and only then will the IRT allow the study treatment to be unblinded.
    - If eligible, participants may enter the OLE phase (Sections 6.7.2 and 6.7.3).
3. The required number of PFS events have been observed and the primary PFS analysis has been completed.
    - If eligible, all ongoing participants at this time may enter the OLE phase.

6.4. Study Treatment Compliance

Participant compliance with study treatment will be monitored throughout the study. At each applicable study visit (Sections 1.3.1 and 1.3.2), the participant should be asked whether he or she has been compliant with dosing instructions. Compliance will also be assessed by counting returned tablets at the applicable study visits. Any discrepancies will be discussed with the participant and will be recorded in the source documentation. The number of tablets dispensed, and the number of tablets returned will be recorded in the eCRF.

If the participant is not compliant with study treatment dosing, the site must re-educate the participant on proper dosing compliance and its importance. Continued non-compliance may lead to withdrawal of the participant from the study, after consultation between the investigator and the medical monitor/sponsor.

In the case of an overdose, refer to Section 8.4 for instructions.

6.5. Concomitant Therapy

6.5.1. Concomitant Medications and/or Procedures

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of informed consent and/or receives during the study through 30 days after the last dose of study treatment must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates; and
- Dosage information including dose and frequency.

The medical monitor/sponsor should be contacted if there are any questions regarding concomitant or prior therapy. Refer to Section 10.10.3 for the medical monitor contact information.

6.5.1.1. Known Drug Interactions

6.5.1.1.1. Cytochrome P450 Inhibitors and Inducers

Because inhibition of CYP3A4 isoenzymes may increase nirogacestat exposure leading to potential increases in toxicities, the use of known strong/moderate CYP3A4 inhibitors is not allowed throughout the double-blind and OLE study phases and must be stopped at least 14 days prior to the first dose of double-blind study treatment.

Nirogacestat metabolism may be induced when taking strong CYP3A4 inducers resulting in reduced plasma concentrations. Therefore, co-administration of nirogacestat in combination with strong CYP3A4 inducers is not allowed throughout the double-blind and OLE study phases and must be stopped at least 14 days prior to the first dose of double-blind study treatment.

6.5.1.1.2. Cytochrome 3A4 Substrates

Nirogacestat has been shown to increase exposure of a sensitive CYP3A4 substrate, midazolam, by approximately 50% following multiple daily doses of 95 mg QD. The potential for nirogacestat to inhibit CYP3A4 in vivo following BID dosing at 150 mg has not been evaluated in a clinical study. However, using physiological-based pharmacokinetic modeling, nirogacestat was predicted to be a moderate inhibitor of CYP3A4 metabolism when administered at 150 mg BID resulting in increases in midazolam exposures ranging from 2- to 3.3-fold. Therefore, caution should be used when co-administering known CYP3A4 substrates with nirogacestat.

Co-administration of CYP3A4 substrates with a narrow therapeutic index should be avoided if possible. If co-administration is unavoidable, the participant should be monitored closely for toxicity and investigator should consider reducing or titrating the dose of the substrate as necessary.

6.5.1.1.3. Anti-Emetic and Anti-Diarrheal Therapy

The choice of anti-emetic drug(s) and anti-diarrheal drug(s), as well as the duration of treatment, is up to the investigator assuming there is no known or expected drug-drug interaction (DDI). If a DDI is expected, then the drug(s) use must be approved by the medical monitor/sponsor.

6.5.1.1.4. Other Concomitant Therapy

Nonclinical studies suggest that nirogacestat may induce CYP3A4, CYP2B6, CYP2C8 and CYP2C9 enzymes. Drugs which are substrates of these enzymes may have a reduced exposure/efficacy when co-administered with nirogacestat. Dose adjustments of these medications should be considered when appropriate.

The effect of nirogacestat on the exposure of hormonal contraceptives has not been evaluated. However, induction of these CYP enzymes has been associated with reduced plasma exposure of various hormonal contraceptives resulting in reduced efficacy.

Nonclinical studies have indicated that nirogacestat is a substrate for the drug efflux transporter P-glycoprotein (P-gp). Therefore, caution should be used when co-administering the study treatment with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, elacridar, felodipine, mibefradil, nitrendipine, quinidine, ranolazine, talinolol, and valspodar. Nonclinical studies have indicated that nirogacestat may also be an inhibitor of P-gp and may increase the exposure of some P-gp substrates like digoxin, dabigatran, and fexofenadine; participants receiving these medications should be closely monitored.

Co-administration of gastric acid reducing agents such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, etc.) may reduce the absorption of nirogacestat. These drugs should be avoided if possible or, when necessary, administered 2 to 4 hours following the morning dose of study treatment.

6.5.1.2. Excluded/Restricted Concomitant Medications and/or Procedures

Table 3 describes the concomitant medications and/or procedures that are excluded/restricted prior and/or throughout the duration of the study until the termination of study treatment. Contact the medical monitor/sponsor with any questions regarding excluded/restricted medications.

Table 3 Restricted/Excluded Medications and/or Procedures

Medication/Procedure	Restriction/Exclusion Timeframe
• Chronic daily use of NSAIDS for treatment of DT/AF;[1] • Tyrosine kinase inhibitors; • Other antineoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy or other antibodies; and • Any investigational treatment for DT/AF.	• Not allowed after the documented DT/AF progressive disease (inclusion criteria 2) or within 28 days (or 5 half-lives, whichever is longer) prior to first dose of double-blind study treatment; and • Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.
• Strong/moderate CYP3A4 inhibitors; and • Strong CYP3A4 inducers.	• Not allowed within 14 days prior to first dose of double-blind study treatment; and • Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.
• CYP3A4 substrates with a narrow therapeutic index.	• Should be avoided if possible; and • If co-administration is unavoidable, the participant should be monitored closely for toxicity and investigator should consider reducing or titrating the dose of the substrate as necessary.
• Gastric acid reducing agents such as proton pump inhibitors.	• Should be avoided if a reasonable alternative is available; and • If administration is necessary, should be administered 2 to 4 hours after the morning dose of study treatment.
• GS inhibitors; • Anti-Notch antibody therapy; and • Gastric bypass, lap band, or other gastric procedures that would alter absorption.	• No prior use, therapy or procedure is allowed; and • Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.
• Antiarrhythmic medications that are known to prolong the QT/QTcF interval including: Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) antiarrhythmics; • Potentially curative radiotherapy; and • Surgical resection of DT/AF tumors.	• Not allowed at the time of informed consent; and • Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.

Medication/Procedure	Restriction/Exclusion Timeframe
• Delivery of nirogacestat via nasogastric tube or gastrostomy tube.	• Not allowed throughout the double-blind or OLE phases.
• Enrollment in another clinical study with any investigational drug or device.[2]	• Not allowed within 28 days prior to first dose of study treatment; and • Not allowed throughout the duration of the double-blind or OLE phases.

[1]Participants who are receiving chronic NSAIDs as treatment for conditions **other than** DT/AF must be receiving them prior to the documented DT/AF progressive disease (inclusion criteria 2) and must be on a stable dose for 28 days prior to first dose of study treatment.

Occasional use (defined as ≤ 3 days per week) of NSAIDs for the treatment of pain or as an anti-inflammatory in conditions such as headache, arthritis, etc., is allowed throughout the treatment period during the study.

Dose increases of NSAIDs will not be permitted during the treatment period during the double-blind phase of the study.

[2]Participation in an observational study may be allowed on a case-by-case basis with prior medical monitor/sponsor approval.

6.5.1.3. Supportive Care

6.5.1.3.1. Phosphate Supplements

Nirogacestat has been associated with hypophosphatemia which may require phosphate supplementation. The choice of phosphate replacement, as well as the duration, is at the investigator's discretion.

6.5.1.3.2. Palliative Care

During the double-blind and OLE phase of the study, systemic therapy or local therapy to the DT/AF tumors are not permitted.

Medications for the standard management of symptoms or supportive care for the management of the effects of study treatment may be administered at the investigator's discretion; unless they are excluded concomitant medications (Section 6.5.1.2).

Palliative radiation therapy may be permitted in the OLE phase of the study after consultation with the medical monitor/sponsor. Radiation will be limited to non-target lesions only and will be documented in the eCRF and on the Pre-Randomization RECIST v1.1 Calculation Worksheet.

Thus, the following therapies are not permitted during the double-blind or OLE phases of the study:

- Other anti-neoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy or other antibodies;
- Potentially curative radiotherapy;
- Surgical resection of DT/AF tumors; and
- Any other investigational therapy.

6.6. Dose Modification

Every effort will be made to administer study treatment (nirogacestat or placebo) at 150 mg BID. However, dosing will be interrupted and/or dose reduced for the AEs described in Table 4. Study treatment may also be modified to manage other AEs in collaboration with the medical monitor.

If a participant experiences an AE as described in Table 4, hold study treatment until the AE is resolved to ≤ Grade 1 or baseline.

- If the AE is resolved within 14 days, then study treatment should be restarted at the reduced dose as described in Table 4.
- If the AE does not resolve to ≤ Grade 1 or baseline after holding study treatment for 22 days, study treatment may be resumed only after discussion with the medical monitor/sponsor. Refer to Section 10.10.3 for the medical monitor contact details.

Should the same ≥ Grade 3 AE recur at the reduced dose, and the AE is considered related to the study treatment, study treatment may be permanently discontinued following discussion with the medical monitor/sponsor.

An unscheduled visit may be performed at any time during the study. Assessments to be performed at the unscheduled visit will be determined by the investigator.

Table 4 Dose Modifications or Interruptions for Selected Toxicities

Toxicity (NCI CTCAE)	**Intervention**
Gastrointestinal Toxicities	
Grade ≥ 3 diarrhea persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Grade ≥ 3 nausea persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Grade ≥ 3 vomiting persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Reproductive system toxicities	
Grade ≥ 2 premature menopause / primary ovarian insufficiency	Decrease dose to 100 mg BID[2]
Other toxicities	
Grade ≥ 3 skin toxicity[1]	Decrease dose to 100 mg BID
Grade ≥ 3 hypophosphatemia persisting for ≥ 7 days despite maximal replacement therapy and in the absence of symptoms	Decrease dose to 100 mg BID
Any clinically significant Grade ≥ 3 non-hematological toxicities	Decrease dose to 100 mg BID
Grade ≥ 3 hematological toxicities	Decrease dose to 100 mg BID.

Toxicity (NCI CTCAE)	Intervention
Anaphylaxis	Permanently discontinue
Grade ≥ 3 hypersensitivity reaction	Permanently discontinue
Hepatic toxicities	Refer to Section 7.1.1

[1]Refer to the study reference manual for guidelines on managing the AE of skin rash.
[2]A dose reduction is not required for events of premature menopause / primary ovarian insufficiency but may be considered for symptomatic participants based on the individual benefit / risk profile. A dose interruption is not required prior to a dose reduction for reproductive system toxicities.

6.7. Treatment after the End of the Double-Blind Study

6.7.1. Optional Open-Label Extension Phase

Eligible participants will have the option to enter the OLE phase of the study. Refer to the OLE SoA (Section 1.3.2) for study visits and timing of assessments, and Section 4.1.2 and Table 7 for overall design and additional details of the OLE phase.

6.7.2. Inclusion Criteria - Open-Label Extension Phase

Participants are eligible to be included in the OLE phase only if all the following criteria apply:

1. Participant is enrolled in the double-blind phase when all the required number of PFS events have been observed and the primary PFS analysis has been completed;

   OR

   Participant is randomized to receive placebo in the double-blind phase and Central Imaging Review determines that the participant has radiographic progressive disease (using RECIST v1.1);

   OR

   Participant is randomized to receive nirogacestat in the double-blind phase and Central Imaging Review determines that the participant has radiographic progressive disease (using RECIST v1.1) but the participant is deriving clinical benefit without significant toxicity (as determined by the investigator).

2. Participant has adequate organ and bone marrow function as outlined in the double-blind inclusion criteria 9 (based off hematology and serum chemistry results within 14 days prior to enrollment in the OLE phase).

3. Participant agrees to use contraception as outlined in the double-blind inclusion criteria 11.

4. Participant is capable of giving signed informed consent specific to the OLE phase, as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

6.7.3. Exclusion Criteria - Open-Label Extension Phase

Participants are excluded from the OLE phase of the study if any of the following criteria apply:

1. Participant requires surgery to prevent organ dysfunction.
2. Participant has prematurely discontinued from the double-blind phase for any reason other than radiographic progressive disease (as determined by Central Imaging Review using RECIST v1.1).
3. Participant developed a concurrent illness/condition that, in the opinion of the investigator, would represent a risk to overall health if they enroll in this study.
4. Participant has initiated a new treatment for DT/AF including tyrosine kinase inhibitors, other antineoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy or other antibodies; and/or any investigational treatment for DT/AF after the Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

It may be necessary for a participant to permanently discontinue study treatment (nirogacestat or placebo) early. In this case, the participant will return to the site for an EOT visit and a post dose follow-up visit (refer to SoA tables in Section 1.3 for a complete list of required assessments to be conducted).

Reasons for discontinuation of study treatment early may include:

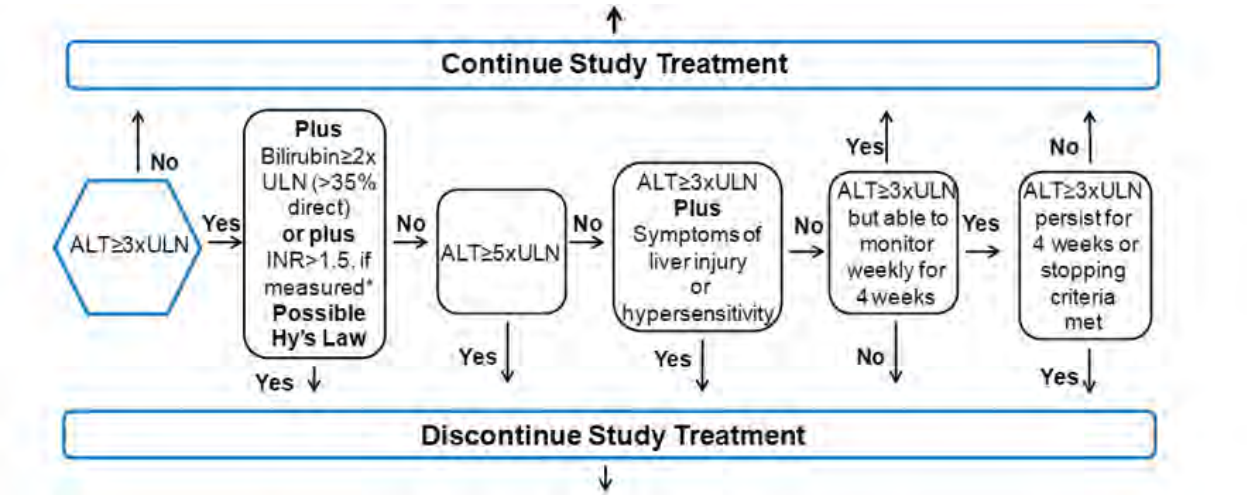
- Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1) in the double-blind phase and the participant does **not** enter the OLE phase;
- Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1);
- The investigator determines the participant is experiencing clinical progression which is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF;
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the requirements of the protocol;
- Participant's study treatment is unblinded for safety reasons or any reason other than radiographic progressive disease as determined via central review (Section 6.3.2.1);
- Any SAE (refer to Section 10.3.2 for SAE criteria), clinically significant AE (refer to QTcF stopping criteria, Section 7.1.2), severe laboratory abnormality (refer to liver chemistry stopping criteria, Section 7.1.1), any grade ≥ 3 hypersensitivity reaction, anaphylaxis, Section 6.6), intercurrent illness, or other medical condition which indicates to the investigator that continued participation is not in the best interest of the participant;
- Pregnancy (refer to Sections 8.3.5 and 10.4 for additional details);
- Requirement of prohibited concomitant medication or procedure (Section 6.5.1.2);
- Participant failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the sponsor or the regulatory authority.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Figure 1 or if the investigator believes that it is in the best interest of the participant.

Figure 1 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm

- **If participant is to be monitored weekly, must refer to Liver Safety: Suggested Actions and Follow-up Assessments (Section 10.6)**



- **Must refer to Liver Safety: Suggested Actions and Follow-up Assessments (Section 10.6)**
- **Report as an SAE if possible Hy's Law case:** ALT ≥ 3xULN and Bilirubin ≥ 2xULN (> 35% direct) or INR > 1.5, if measured*

*INR value not applicable to participants on anticoagulants

Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

7.1.2. QTcF Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECGs printed at the time of collection must be documented. Any new clinically relevant finding must be reported as an AE.

A participant who meets either of the following bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTcF > 500 msec
- Change from baseline of QTcF > 60 msec

Table 5 describes the discontinuation criteria for participants with underlying bundle branch block.

Table 5 Bundle Branch Block Discontinuation Criteria

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

See the SoA for data to be collected at the time of study treatment discontinuation and follow-up, and for any further evaluations that need to be completed.

7.1.3. Pregnancy

A female participant who becomes pregnant will be withdrawn from study treatment. See Section 10.4 and Section 8.3.5 for additional details.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, the EOT visit should be conducted. See SoA (Section 1.3) for specific data to be collected at the time of study discontinuation, as well as follow-up for any further evaluations that need to be completed.
- If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested. The sponsor must be notified if the participant requests destruction of sample, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts must be documented in the participant's medical record.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the medical monitor/sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment (nirogacestat or placebo).
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria (Sections 5.1, 5.2, 6.7.2, and 6.7.3). The electronic data capture (EDC) will capture all participants who sign the ICF, including all screen-failures.
- The amount of blood collected from each participant will be approximately 218 mL **each year** throughout the double-blind phase and 180 mL **each year** throughout the OLE phase. This does not include any extra assessments that may be required for unscheduled assessments. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In the event that a study site or participant is unable to complete a study visit or procedure due to restrictions caused by a public health emergency such as COVID-19, the following accommodations may be allowed temporarily with prior approval from the medical monitor / sponsor. Any deviations from the study protocol due to a public health emergency should be documented in the source data and eCRF and reported to the IRB/EC in accordance with their reporting requirements.
    - If a study participant cannot attend a study visit onsite due to a public health emergency, they may be able to attend a local hospital/clinic or arrange for a telehealth or home healthcare visit.
    - Clinical laboratory assessments may be performed locally with results and local laboratory normal values entered into the eCRF.
    -
    - Electrocardiograms may be performed locally. If ECGs are performed locally, ECG tracings should be collected and the investigator (or designee) assessment should be documented. Every effort should be made to perform ECGs in triplicate; however, a single ECG will be allowed if necessary due to a public health emergency.
    - Study imaging including CT and/or MRI should be performed per the schedule in the SoA at a qualified imaging facility; however, local imaging may be allowed

with prior sponsor approval. Local imaging will need to be uploaded for Central Imaging Review.

Table 6 Double-Blind Phase Study Visits

This table supplements the SoA and highlights key study visit reminders. Refer to the double-blind phase SoA table (Section 1.3.1) for the complete list of study assessments, and the study reference manual for study visit checklists which will include the recommended sequence of assessments for each study visit.

Screening (double-blind phase)
Operational visit reminders: • Refer to the SoA table for a complete list of required study assessments (Section 1.3.1). • Screening assessments may occur up to 28 days prior to first dose of study treatment with a minimum screening period of 14 days to allow for participant completion of the screening and baseline ePRO assessments. • An extension to the screening period may be permitted on a case-by-case basis following discussion between the investigator and the medical monitor / sponsor (refer to Section 10.10.3 for medical monitor contact information). The reason(s) for the extension must be clearly documented. • The date the participant signs the ICF will be Day 1 of the screening period. • The participant will be assigned a study identification number at the screening visit. This number can be found on the screening laboratory requisition form in the Subject Requisition Binder and will be entered into the IRT at the screening visit. This participant identification number will be utilized for the duration of the study. ePRO reminders: • On Day 1 of the screening period, participants will receive training on how to use the home ePRO device (provided by the sponsor), which will include a practice questionnaire to be completed prior to the participant leaving the site. The participant will then begin the screening PRO assessments later that same day. Refer to Table 8 for details on the ePRO assessment administration schedule. • If the participant screen fails during the screening period, they should be reminded to return the device back to the site. Imaging reminders: Pre-randomization scans: • To meet inclusion criteria 2, participants must have had two scans (MRI or CT) that show ≥ 20% disease progression as measured by RECIST v1.1 within 12 months of the

screening visit scan (which will serve as the participant's baseline scan for the study). Pre-randomization scans will be evaluated locally (not subject to central review).

- As part of documenting that participants have satisfied inclusion criteria 2, sites are required to complete a Pre-Randomization RECIST v1.1 Calculation Worksheet (provided by the sponsor) (Section 8.1.1.1). The worksheet must be submitted to the sponsor's designee during the screening period as soon as the data are available to complete the worksheet. All worksheets must be received no later than 7 days prior to C1D1 to allow for review prior to randomization (refer to study reference manual).

Screening visit scan(s):

- An MRI scan (no contrast required) will be acquired during the 28-day screening period, prior to the participant's first dose of study treatment.
- A CT scan (contrast required unless contraindicated) is only required if CT is the chosen modality for RECIST v1.1 tumor assessment (modality to be determined by the investigator). If CT is the chosen modality for RECIST v1.1, then a CT scan must be acquired during the 28-day screening period, prior to the participant's first dose of study treatment.
- Whichever modality is used at screening (CT or MRI) for tumor assessment (RECIST v1.1), the same modality must continue to be used at each subsequent visit throughout the study.
- If applicable, CT and MRI assessments may be conducted on the same day. However, MRI with no contrast must be performed prior to CT with contrast.
- The scan(s) conducted at the screening visit will serve as the participant's baseline for the study. Therefore, scans should be submitted to the central imaging core laboratory as early in the screening period as possible to confirm scan quality is acceptable for analysis prior to randomization. The scan(s) conducted at the screening visit should also be read locally.
- Standard of care scan(s) acquired prior to participant signing ICF may be used as screening visit scan(s) if obtained within 28 days of the first dose of study treatment and the quality of the scans are acceptable for analysis (as determined by central imaging core laboratory). These standard of care scans will then be collected, stored, and documented as the screening visit scan(s). No other pre-enrollment images will be collected for central reading.

<u>Tumor biopsy reminders:</u>

- Core needle biopsy is only required if archival tissue is not available for study procedures (Section 8.1.3).
- If tumor biopsy and MRI are performed during the same study visit, the biopsy must be done after MRI.

- Tumor biopsy will be reviewed centrally to reconfirm diagnosis, but participant enrollment is not dependent on central review.

Baseline and Cycle 1 Day 1 (double-blind phase)

Operational visit reminders:

- Refer to the SoA table for a complete list of required study assessments (Section 1.3.1).
- The baseline visit may occur up to 48 hours prior to first dose of study treatment (nirogacestat or placebo).
- Cycle 1 Day 1 will be defined as the first dose of study treatment.
- The following baseline assessments are to be conducted prior to the first dose of study treatment:
    - Physical examination and ECOG performance status (Section 8.2.2);
    - Vital signs and weight (Section 8.2.4);
    - Pre-dose 12-Lead ECGs (Section 8.2.3);
    - Urinalysis and urine pregnancy for women of childbearing potential (WOCBP) (Section 8.2.6);
    - Blood draws for safety lab parameters, hormone levels, (Sections 8.2.5 and 10.2), genotyping (Section 8.7) and optional pharmacogenomic sample (Sections 8.8 and 10.5);
    - Concomitant medication and AE/SAE review; and
    - Single pre-dose PK blood draw.
- After all of the pre-dose baseline assessments (as noted above) have been completed and the participant's eligibility has been confirmed (Sections 5.1 and 5.2), the participant will be randomized and the first dose of study treatment (150 mg) will be administered at the site.
- The following baseline assessments are to be conducted after the first dose of study treatment:
    - Triplicate 12-Lead ECGs (Section 8.2.3) to be conducted approximately 1-hour post-dose;
    - PK sampling (Section 8.5) to be conducted at 0.25-, 0.5-, 1-, 1.5-, 2-, 3-hours post-dose; and
    - 3-hour observation period following the first dose of study treatment.

ePRO reminders:

- Baseline ePRO assessments will begin 7 days prior to the scheduled Cycle 1 Day 1 study visit.
- Refer to Table 8 for details on the ePRO assessment administration schedule.

Cycle 1 Day 8, 15, 22, and Cycle 2 Day 28 (double-blind phase)

Operational visit reminders:

- Refer to the SoA table for a complete list of required study assessments (Section 1.3.1).
- Visit windows are ± 2 days.
- At Cycle 1 Day 8, triplicate 12-Lead ECGs are required 1-hour (± 10 minutes) post-dose. Therefore, study treatment must be taken in the clinic at this visit.
- A trough PK sample is required at each study visit. Therefore, the evening before the study visit, the participant will record the exact time study treatment was taken in the home ePRO device. Participant will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.
- Urine pregnancy tests for participants of WOCBP must be performed at Cycle 1 Day 22 and Cycle 2 Day 28.

Cycle 4 Day 1, Cycle 7 Day 1 and Every 3 Cycles (double-blind phase)

Operational visit reminders:

- Refer to the SoA table for a complete list of required study assessments (Section 1.3.1).
- Visit windows are ± 7 days.
- A trough PK sample is required at each study visit. Therefore, the evening before the study visit, the participant will record the exact time study treatment was taken in the home ePRO device. Participant will not take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.
- The site should submit scans to the central imaging core laboratory for Central Imaging Review as soon as possible following the study visit. Scans should also be read locally per RECIST v1.1.
- MRI for tumor volume is required starting with Cycle 7 and then every 6 cycles throughout the study. If MRI for tumor volume assessment and CT for tumor assessment (RECIST v1.1) are conducted on the same day, MRI with no contrast must be performed prior to CT with contrast.
- Beginning at the Cycle 4 Day 1 visit, participants will return all used / unused study treatment, and will be dispensed new study treatment using the IRT at every applicable

study visit. Accountability must by counting the returned study treatment tablets and document compliance in the eCRF.

End of Treatment (EOT) (double-blind phase)

The EOT visit will occur when:

1. A participant has met the study endpoint of radiographic progression using RECIST v1.1 (determined by Central Imaging Review) or is experiencing clinical progression as assessed by the investigator;
2. Participant prematurely discontinues study treatment for any other reason;
3. Study is stopped by the sponsor for any reason; or
4. All required number of PFS events have been observed and the primary PFS analysis has been completed.

Operational visit reminders:

If Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1) during the double-blind phase of the study, the following steps will occur:

1. Site will be notified by the central imaging core laboratory that Central Imaging Review has as determined the participant has radiographic progressive disease (using RECIST v1.1).
2. Participant will return to the site for an EOT visit within 14 days of the site receiving the radiographic progressive disease notification from the central imaging core laboratory.
3. Participant should be instructed to remain on study treatment until the EOT visit (if possible).
4. All double-blind EOT study assessments will be completed in a blinded manner (refer to SoA table Section 1.3.1 for complete list of assessments).
5. All ongoing AEs/SAEs from the double-blind phase will be assessed for causality by the investigator (or qualified designee) in a blinded manner and recorded in the eCRF.
6. Sponsor designee will confirm that the above criteria have been met and only then will the IRT allow the participant's study treatment assignment to be unblinded.
7. Eligible participants may enter the OLE phase at this time. The EOT visit should be conducted on the same day as, or 24 hours prior to, the C1D1 visit for the OLE phase. A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1.

If a participant discontinues study treatment for any reason other than radiographic progressive disease as determined via central review the following steps will occur:

1. Participant will return to the site for an EOT visit as soon as possible.
2. Participant should be instructed to remain on study treatment until the EOT visit (if possible).
3. All double-blind EOT study assessments will be completed in a blinded manner (refer to SoA table Section 1.3.1 for complete list of assessments).
4. The participant's study treatment allocation will **not** be unblinded.

Imaging reminders:

5. Scan(s) only required if not performed within the past 3 months.

Tumor biopsy reminders:

6. Tumor biopsy at EOT visit is optional if the participant consented for pharmacogenomic research (Section 8.1.3).
7. If tumor biopsy and MRI are performed during the same study visit, the biopsy must be done after MRI.

Follow-Up (double-blind phase)

Visit is applicable only if participant is **not** continuing onto the optional OLE phase.

Operational visit reminders:

- Participant will return to the site for the follow-up visit 30 days (+7 days) after the last dose of study treatment.
- ePROs are to be completed 7 days prior to the scheduled follow-up visit (Table 8).
- Participant will return the home ePRO device.

Monthly Wellness Checks (double-blind phase)

- Monthly telephone or email contact is required throughout the study.
- May be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit.
- Refer to Section 8.2.7.

Monthly Urine Pregnancy Tests (double-blind phase)

- Assessment applicable to women of child-bearing potential (WOCBP) only.

• In between study visits, participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to study reference manual for additional details). • Refer to Section 8.2.6.
Monthly PRO Assessments (double-blind phase)
• The home ePRO device (supplied by the sponsor) will be programmed to prompt the participant to complete the questionnaires monthly throughout the study, and always prior to a study visit when applicable. • Refer to Section 8.1.2 and Table 8.
Unscheduled Visits (double-blind phase)
Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Open-Label Phase Study Visits

This table supplements the SoA and highlights key study visit reminders. Refer to the OLE phase SoA table (Section 1.3.2) for the complete list of study assessments, and the study reference manual for study visit checklists which will include the recommended sequence of assessments for each study visit.

Cycle 1 Day 1 (OLE phase)
The OLE phase allows eligible participants to receive open-label study treatment (nirogacestat). Refer to Sections 6.7.2 and 6.7.3 for OLE specific eligibility criteria. The OLE Cycle 1 Day 1 visit should be conducted on the same day as, or within 24 hours after, the double-blind EOT visit. A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1. Operational visit reminders: • All double-blind EOT visit assessments described in the double-blind SoA (Section 1.3.1) will be conducted prior to unblinding the participant's study treatment assignment and prior to the first dose of open-label study treatment. The following OLE baseline assessments must be conducted prior to administration of the first dose of open-label study treatment: o Obtain participant's consent using OLE phase specific ICF; o Confirm participant meets all I/E criteria specific to the OLE phase (refer to Sections 6.7.2 and 6.7.3); o Draw blood for hematology and serum chemistry safety assessments for local lab processing (only if labs not done within the past 14 days); hormone levels do not need to be repeated if performed at EOT for the double-blind phase of the study. o *Note: if hematology and serum chemistry safety labs have not been conducted within the past 14 days prior to baseline, an additional blood draw will be required for same day local laboratory processing to reconfirm adequate organ and bone marrow function (refer to OLE inclusion criteria 2)* o Enroll participant in the OLE phase using the IRT and dispense study treatment; o Draw a single pre-dose PK blood draw (only applicable for participants who were previously randomized to placebo in the double-blind phase); • After the OLE pre-dose baseline assessments (as noted above) have been completed, the first dose of open-label study treatment will be administered at the site for participants

who were previously randomized to placebo in the double-blind phase. Participants who were randomized to nirogacestat may take their first dose at home.

- The following OLE baseline assessments will be conducted after the first dose (only applicable for participants who were previously randomized to placebo in the double-blind phase):
  - Conduct serial PK sampling at 0.25-, 0.5-, 1-, 1.5-, 2-, and 3-hours post-dose;
  - Conduct triplicate 12-Lead ECGs approximately 1-hour post-dose; and
  - Complete the 3-hour observation period following the first dose of study treatment.

Cycle 1 Day 8, 15, 22 and Cycle 2 Day 28 (OLE phase)

Visits are applicable only to participants who were previously randomized to receive placebo in the double-blind phase.

Operational visit reminders:

- Refer to the SoA table for a complete list of required study assessments (Section 1.3.2).
- Visit windows are ± 2 days.
- At Cycle 1 Day 8, triplicate 12-Lead ECGs are required 1-hour (± 10 minutes) post-dose. Therefore, study treatment must be taken in the clinic at this visit.
- A trough PK sample is required at each study visit. Therefore, the evening before the study visit, the participant will record the exact time study treatment was taken in the home ePRO device. Participant will not take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.
- Urine pregnancy tests for participants of WOCBP must be performed at Cycle 1 Day 22 and Cycle 2 Day 28.

Cycle 4 Day 1 and Every 3 Cycles (OLE phase)

Visits are applicable to all participants.

Operational visit reminders:

- Refer to the SoA table for a complete list of required study assessments (Section 1.3.2).
- Visit windows are ± 7 days.
- CT or MRI scan required every 3 cycles until Cycle 13 Day 1, and then required every 6 cycles thereafter.
- A trough PK sample is required at each study visit. Therefore, the evening before the study visit, the participant will record the exact time study treatment was taken in the home ePRO device. Participant will not take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.

- The site should submit scans to the central imaging core laboratory for Central Imaging Review as soon as possible following the study visit. Scans should also be read locally per RECIST v1.1.
- Beginning at the Cycle 4 Day 1 visit, participants will return all used / unused study treatment, and will be dispensed new study treatment using the IRT at every applicable study visit. Accountability must be performed on the returned tablets.

End of Treatment (EOT) (OLE phase)

The EOT visit will occur when:

- A participant has met the study endpoint of radiographic progression using RECIST v1.1 (determined by Central Imaging Review);
- The investigator determines that the participant is experiencing clinical progression defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF;
- Participant discontinues study treatment for any reason;
- Study is stopped by the sponsor for any reason;
- Participant qualifies for Sponsor's Continued Access Plan; or
- Nirogacestat becomes commercially available.

Operational visit reminders:

- Participants will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (Section 1.3.2).
- If possible, participants should be encouraged to remain on study treatment until the EOT visit.

Follow-Up (OLE phase)

Visit is applicable only if participant is **not** transitioning directly to commercial nirogacestat (or sponsor's Continued Access Plan) at the time of discontinuation.

Operational visit reminders:

- Participant will return to the site for the follow-up visit 30 days (+7 days) after the last dose of study treatment.
- ePROs to be completed 7 days prior to the scheduled follow-up visit (Table 9).
- Participant will return the home ePRO device.

Monthly Wellness Checks (OLE phase)

• Monthly telephone or email contact is required throughout the study. • May be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit. • Refer to Section 8.2.7.
Monthly Urine Pregnancy Tests (OLE phase)
• Assessment applicable to women of child-bearing potential (WOCBP) only. • In between study visits, participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to the study reference manual for additional detail). • Refer to Section 8.2.6.
Monthly / Quarterly PRO Assessments (OLE phase)
• The home ePRO device (supplied by the sponsor) will be programmed to prompt the participant to complete the questionnaires monthly for the first year and then quarterly thereafter, and always prior to a study visit when applicable. • Refer to Section 8.1.2 and Table 9.
Unscheduled Visits (OLE phase)
Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1. Tumor Imaging

Central Core Imaging Laboratory:

Sites will submit all CT and MRI scans to the central imaging core laboratory for Central Imaging Review. The purpose of the Central Imaging Review is to provide an independent, unbiased and objective review of the CT and MRI data throughout the study.

Sites will be provided an Imaging Acquisition Manual and an Imaging Submission Manual, which describe the imaging methods and submission process that must be followed.

All image data submitted to the central imaging core laboratory must be de-identified prior to submission. The participant identifiers on the image data must be consistent with all study-related documents throughout the study. See imaging manuals for details on the de-identification requirements.

Site Qualification and Training:

Before sites are activated and able to enroll participants, they will be trained on the protocol imaging requirements and provided guidance on how to submit scans.

In addition, all sites are required to submit qualification scans to the central imaging core laboratory prior to study initiation. These qualification scans will be evaluated for image quality and adherence to study protocol parameters. Once the site qualification scans have passed image quality control, a site qualification certificate will be issued. The site must file this certificate with their site study documents.

On Study Scans:

It is important for the site to make every effort to use the same scanner(s) that have been qualified (as described above) throughout the double-blind and OLE phases of the study. If the same scanner is unavailable, another qualified scanner of the same model should be used with the same settings. Study imaging including MRI and/or CT should be performed per the schedule in the SoA at a qualified imaging facility; however, in the event that a study site or participant is unable to complete a study visit or procedure due to restrictions caused by a public health emergency such as COVID-19, local imaging may be allowed with prior sponsor approval.

The screening visit scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review. However, participant enrollment will not be dependent on central review.

Standard of care scan(s) acquired prior to the participant signing ICF may be used as the participant's screening visit scans if they were obtained within 28 days of the first dose of double-blind study treatment administration. The scan(s) will then be collected, stored, and documented as the screening visit scans. No other pre-enrollment images will be collected for central reading.

All scans should be submitted to the central imaging core laboratory as soon as possible after acquisition. This will allow the central imaging core laboratory to assess the scans for quality and query the site if necessary. If the scans are deemed unacceptable for analysis, the site will be queried, and a replacement scan will be requested.

If necessary, both CT and MRI assessments may be conducted on the same day, but MRI with no contrast must be performed prior to the CT with contrast.

Whenever disease progression is suspected (e.g., symptomatic deterioration) throughout the study, unscheduled scans may be acquired and submitted to the central imaging core laboratory for Central Imaging Review.

8.1.1.1. Pre-Randomization RECIST v1.1 Calculation Worksheet

As part of documenting that participants have satisfied inclusion criteria 2 for the double-blind phase, sites are required to complete the Pre-Randomization RECIST v1.1 Calculation Worksheet (provided by the sponsor). The worksheet must be submitted to the sponsor's designee during the screening period as soon as the data are available to complete the worksheet, and no later than 7 days prior to C1D1 to allow for review prior to randomization.

8.1.1.2. Tumor Assessment Using RECIST Version 1.1 Criteria

Tumor assessment for primary and secondary endpoints (PFS and ORR, respectively) as measured by CT (contrast required unless contraindicated) or MRI (no contrast required), will be evaluated by Central Imaging Review for all participants using RECIST v1.1 (Eisenhauer, 2009) at the following timepoints:

- At the double-blind and OLE phases as specified in the SoA (Sections 1.3.1 and 1.3.2); and
- Whenever disease progression is suspected (e.g., symptomatic deterioration).

The imaging modality will be determined by the investigator and the same imaging modality used to measure the identified and reported lesion at screening in the double-blind phase must be used at each subsequent visit throughout the double-blind and OLE phases.

The location of the target tumor(s) will be selected by the investigator as the basis for inclusion in the trial and will be documented on the Pre-Randomization RECIST v1.1 Calculation Worksheet. The target tumor(s) will be provided to Central Imaging Review and will be used for assessment of the primary endpoint.

While tumor assessments performed by Central Imaging Review will be used for primary and secondary endpoints, tumor measurements will also be performed locally using RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet as specified in the SoA (Sections 1.3.1 and 1.3.2) and whenever disease progression is suspected (e.g., symptomatic deterioration).

8.1.1.3. Volumetric Assessment

Tumor volume assessment and T2 hyperintensity imaging will be acquired only by MRI and only applicable in the double-blind phase of the study as specified in the SoA (Section 1.3.1). Refer to the Imaging Acquisition Manual for details.

8.1.2. Definition and Assessment of Clinical Progression

Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.

The date of clinical progression will be the earliest date of onset or worsening of symptoms resulting in a global deterioration of health status. In addition, AEs and SAEs associated with clinical progression and concomitant medications and procedures initiated for the treatment of DT/AF within 30 days of the last dose of study treatment will be documented in the eCRF. A clinical progression narrative will also be developed by the PI for events of clinical progression which will be documented in EDC and include a description of onset or worsening of symptoms resulting in a global deterioration of health status, the location of progressing lesions, and evidence of vital structure involvement (as reported by the PI), as applicable.

When disease progression is suspected (e.g., symptomatic deterioration), imaging should be performed and submitted to the central imaging core laboratory for Central Imaging Review. If progressive disease is not determined radiologically via central review of RECIST v1.1 per Section 8.1.1.2, but the participant meets the definition of clinical progression, the participant may be discontinued for clinical progression. Study participants who discontinue due to clinical progression will NOT be unblinded at the EOT visit and will NOT be eligible for participation in the optional OLE phase.

Imaging data from participants who discontinue due to clinical progression will be evaluated for changes in tumor characteristics or involvement of vital organ structure at the site of progression, which may include:

1. Individual tumor measurements including all available planes of measurement
2. Volumetric MRI, if available
3. T2 hyperintensity, if available

Events of clinical progression will be adjudicated by an independent blinded central clinical review committee which will qualify events of clinical progression for inclusion in the primary analysis of PFS prior to study unblinding according to a Central Clinical Review Charter.

8.1.3. Patient-Reported Outcomes

Participants will complete the PRO questionnaires using their home ePRO devices (supplied by the sponsor). These home ePRO devices will be provided to participants at the screening visit and will be returned to the site at the end of study participation.

The home ePRO device will be programmed to always administer the PROs in a particular order and at specific timepoints throughout the study (refer to Table 8 and Table 9).

The following PRO assessments will be conducted during the double-blind phase:

- Screening PRO assessment:
    - On Day 1 of the screening visit, participants will receive training by the site staff on how to use the home ePRO device, which will include a practice questionnaire to be completed by the participant prior to leaving the site.
    - Participants will then begin the screening PROs assessments that same day.
    - The Patient Global Impression of Change (PGIC) is intentionally omitted from the screening PRO assessments.
- Baseline PRO assessment:
    - The baseline PRO assessments will begin 7 days prior to the Cycle 1 Day 1 visit.
    - The PGIC is intentionally omitted from the baseline PRO assessments.
- Monthly PRO assessments are required throughout the study (Cycle 2, 3, 4 and on).

The following PRO assessments will be conducted during the OLE phase:

- Monthly PRO assessments are required for the first year (Cycle 2-12).
- Quarterly PRO assessments are required after the first year (Cycle 13, 16, 19 and on).

Table 8 Double-Blind Phase: PRO Assessment Administration Schedule

PROs	**Screening PRO Assessments** *First 7 days of screening period*							**Baseline PRO Assessments** *7 day prior to baseline visit*							**Base-line Visit**	**Monthly PRO Assessments** *7 days prior to Cycle X/FU (X = Cycles 2, 3, 4 & on)*							**Cycle X/FU Visit**
	d 1	**d 2**	**d 3**	**d 4**	**d 5**	**d 6**	**d 7**	**d -7**	**d -6**	**d -5**	**d -4**	**d -3**	**d -2**	**d -1**		**d -7**	**d -6**	**d -5**	**d -4**	**d -3**	**d -2**	**d -1**	
GODDESS (symptom scale)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
BPI short form	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PROMIS PF short form 10a plus 3 additional items from the PROMIS item banks							X							X								X	
GODDESS (impact scale)							X							X								X	
EORTC QLQ-C30							X							X								X	
PGIS							X							X								X	
PGIC																						X	

BPI = brief pain inventory; d = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; PGIC = patient global impression of change; PGIS = patient global impression of severity; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function

Table 9 OLE Phase: PRO Assessment Administration Schedule

PROs	**Monthly PRO Assessments** *7 days prior to Cycle X (X = Cycles 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12)*							**Cycle X**	**Quarterly PRO Assessments** *7 day prior to Cycle X (X = Cycles 13, 16, 19, 22 & on)*							**Cycle X**	**Follow-Up PRO Assessments** *7 days prior to the FU visit*							**FU Visit**
	d -7	**d -6**	**d -5**	**d -4**	**d -3**	**d -2**	**d -1**		**d -7**	**d -6**	**d -5**	**d -4**	**d -3**	**d -2**	**d -1**		**d -7**	**d -6**	**d -5**	**d -4**	**d -3**	**d -2**	**d -1**	
GODDESS (symptom scale)	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
BPI short form	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PROMIS PF short form 10a plus 3 additional items from the PROMIS item banks							X								X								X	
GODDESS (impact scale)							X								X								X	
EORTC QLQ-C30							X								X								X	
PGIS							X								X								X	
PGIC							X								X								X	

BPI = brief pain inventory; d = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; PGIS = patient global impression of severity; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function

8.1.3.1. GODDESS

The GOunder/DTRF DEsmoid Symptom/Impact Scale (GODDESS) tool was developed by Memorial Sloan Kettering Cancer Center (MSKCC) and Desmoid Tumor Research Foundation (DTRF) to measure signs and symptoms of desmoid tumors and their impact on patients' lives. The tool consists of items assessing the severity of key signs and symptoms (11 items), including pain, fatigue, swelling, muscle weakness, difficulty moving, and tumor location-specific signs/symptoms; the impact of these symptoms on functioning and daily living (17-items).

The signs and symptoms items are evaluated on an 11-point numeric rating scale (NRS) from 0-10 to measure severity from "none" to "as bad as you can imagine," with a 24-hour recall period. The impact items are evaluated either on an 11-point NRS to measure severity, or a 5-point Likert Scale ranging from "none of the time" to "all of the time" to measure frequency, with a 7-day recall period.

8.1.3.2. BPI Short Form

The Brief Pain Inventory (BPI) short form is a measurement tool for assessing clinical pain and allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. The short form version of the BPI consists of 9 questions and will utilize an 11-point NRS from 0-10 with a 24-hour recall period.

8.1.3.3. PROMIS PF Short Form 10a Plus 3 Additional Items from PROMIS Item Banks

The Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) instruments measure self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands.

The PROMIS PF short form 10a version 2.0 will be used in this study with a 7-day recall period. This PRO assessment consists of 10 questions and was constructed with a focus on representing the range of the trait and the content of the item bank, as well as mapping the questions in the instrument to qualitative evidence of the physical function concepts important to patients. To supplement the PROMIS PF short form 10a, 3 additional questions representing other elements of physical function found to be important to patients, were selected from the PROMIS Physical Function, Upper Extremity, and Ability to Participate item banks.

8.1.3.4. EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-30) is a quality of life (QoL) questionnaire used for assessing the health-related quality of life of cancer patients participating in international clinical trials.

EORTC QLQ-C30 version 3.0 will be used in this study with a 7-day recall period. It consists of 30 questions overall with a 4-point scale and incorporates 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms

commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of disease.

8.1.3.5. PGIS

The Patient Global Impression of Severity (PGIS) is a single item scale that evaluates the participant's perception of the overall severity of their desmoid related symptoms over the past week on a 4-point scale ranging from "none" to "severe." The PGIS will have a 7-day recall period.

8.1.3.6. PGIC

The Patient Global Impression of Change (PGIC) is a single item scale that evaluates the participant's perception of the overall change in their overall status since the start of the study treatment on a 7-point scale ranging from "very much better" to "very much worse." The PGIC will have a 7-day recall period.

8.1.4. Tumor Biopsy

For all participants:

- Tumor samples will be used to reconfirm desmoid diagnosis for all participants. However, participant enrollment will not be dependent on central review.
- Additionally, archival or fresh tumor biopsies collected at screening will be used for somatic genotyping (unless prohibited by local regulations) (Section 8.7).
- Ideally, 2 cores will be collected during the screening period (prior to study treatment initiation).
- Archival tissue may be used in place of fresh tumor biopsies only if the tissue has been well preserved and there is a sufficient amount of tissue available[1].
- When applicable, fresh tumor biopsies must be taken after MRI if both of these assessments occur at the same visit.

For participants consenting to optional pharmacogenomics research:

- For participants consenting to the optional pharmacogenomics research, an additional tumor biopsy will be collected at the EOT visit.
- Refer to Section 8.8 for details on biomarkers.

[1]Tumor specimens will be stored as formalin-fixed, paraffin embedded (FFPE) blocks at room temperature. If the FFPE block cannot be made available, approximately 20 unstained slides should be used in place of 2 cores.

Instructions for handling, processing and shipment of tumor biopsies are provided in the central laboratory manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Demographics Data and Medical History

Demographic data will include age or date of birth, sex, and self-reported race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (i.e., WOCBP or no WOCBP); history of alcohol consumption (i.e., presence or absence); and collection of concomitant medications. For women, the medical history should also include a detailed menstrual history including the date of the last menstrual cycle and any history of amenorrhea, menstrual irregularities, or infertility. Any history of infertility in male participants should also be recorded as part of the medical history.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator.

8.2.2. Physical Examinations and Eastern Cooperative Oncology Group Performance status

Physical examinations, as well as height/weight, and assessment of ECOG performance status (Section 10.7) will be required throughout the study as described in the SoA. Height to be measured at screening only.

A physical examination should include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

Investigators must pay special attention to clinical signs related to previous serious illnesses, and changes from baseline will be recorded in the source documentation. New or worsened clinically significant abnormalities must be recorded as AEs on the eCRF page.

Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

8.2.3. Electrocardiograms

Triplicate 12-Lead ECGs readings (approximately 2-3 minutes apart and averaged) will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals, at the timepoints described in the SoA. Prior to the ECG assessments, participants should rest in a semi-recumbent supine position for at least 5 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the source documentation at the site.

Refer to Section 7.1.2 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

8.2.4. Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed throughout the study as described in the SoA.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure, respiratory rate, pulse rate and body temperature should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.5. Clinical Safety Laboratory Assessments

All protocol-required, central laboratory assessments as defined in Section 10.2, must be conducted in accordance with the central laboratory manual and the SoA. Please note, ALL participants, regardless of their gender or childbearing potential, are required to have hormone level assessments per the SOA (Section 1.3).

In the event of a public health emergency, clinical laboratory assessments may be performed locally with results and local laboratory normal values entered into the eCRF.

The investigator must review the central laboratory report, document this review, and record any clinically relevant changes occurring during the study on the AE page of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with abnormal values considered to be clinically significant during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF, and the local laboratory report must be assessed by the investigator and included in the participant’s medical records.

8.2.6. Pregnancy Testing

Pregnancy testing will only be required for women of childbearing potential (WOCBP) (refer to Section 10.4 for definition of WOCBP and additional details on contraceptive guidelines and collection of pregnancy information).

A negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (prior to first dose of double-blind study treatment) will be required to meet study entry criteria.

Monthly urine pregnancy tests will be required for WOCBP throughout the duration of the double-blind and OLE phases. In between study visits, participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient to the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to study reference manual for additional detail).

Serum pregnancy tests may be conducted in place of urine pregnancy tests throughout the study if required by local regulations.

8.2.7. Monthly Wellness Checks

Monthly telephone or email contact is required throughout the double-blind and OLE phases of the study and may be replaced by a face-to-face interaction when study visits occur and the information can be obtained during the visit.

A copy of the telephone report or email must be documented in the source documentation. Email must not replace direct follow-up by phone or in-clinic visits for clinically significant AEs or other emergent issues. Adverse events and concomitant medications changes will be captured in the associated eCRFs.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE, SAE, adverse reaction (AR), suspected adverse reaction (SAR), and a suspected unexpected serious adverse reaction (SUSAR) can be found in Section 10.3.

An AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the time of signing ICF until 30 days after the last dose of study treatment at the time points specified in the SoA (Section 1.3) throughout the double-blind and OLE study phases.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as AEs.

All SAEs will be recorded and reported to the sponsor's safety group ('Safety') immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.4. The investigator will submit any updated SAE data to Safety within 24 hours of it being available.

To report the SAE, a paper SAE form must be completed, scanned and emailed to Safety at PV@springworkstx.com. The paper SAE form can be found in the study reference manual. Refer to Section 10.3.4 for more details on reporting SAEs to the sponsor.

Refer to Section 8.3.6 for details on AEs of special interest (AESI) reporting guidelines.

Investigators are not obligated to actively seek AEs and/or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and/or SAEs, and the procedures for completing and transmitting SAE reports are provided in Section 10.3.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and adverse events of special interest (AESI) (as defined in Section 8.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Within 24 hours of receipt of SAE follow-up information, the investigator must complete a paper follow-up SAE form and submit any supporting documentation if requested to Safety. Further information on follow-up procedures is given in Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 30 days after the last dose of study treatment.

If a pregnancy is reported, the investigator must inform the sponsor within 24 hours of learning of the pregnancy by completing a paper pregnancy form and submitting to Safety (refer to Section 10.4 for reporting details).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest (AESI) are selected non-serious and serious AEs that must be reported regardless of relationship to study treatment. Refer to Table 10 for the AESIs identified for this study. AESIs will be followed until resolution or return to baseline.

Serious AESIs must be reported to Safety immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.4.

Non-serious AESIs must be reported to the sponsor (by entering the AESI into the eCRF and submitting a paper SAE/AESI report form to Safety) as soon as possible, but no later than 5 business days of awareness.

Following medical evaluation, sites may be contacted to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event. Please note this table lists known AESI; additional events may be identified during the course of the study.

Table 10 Adverse Events of Special Interest (AESI)

Skin Rash (reported as AESI if clinically significant Grade 2 and all Grade ≥ 3, per CTCAE v. 5)
1. Maculopapular rash
2. Pruritic rash
3. Erythematous rash
4. Folliculitis
5. Hidradenitis suppurativa
Elevated Liver Enzymes (reported as AESI if Grade ≥ 2, per CTCAE v. 5)
1. AST
2. ALT
3. Alkaline Phosphatase

Electrolyte Insufficiency (reported as AESI if Grade ≥ 3, per CTCAE v. 5)
1. Hypophosphatemia
2. Hypokalemia
3. Hypomagnesemia
Drug Reactions (reported as AESI for any grade)
1. Allergic reaction
2. Anaphylaxis
Reproductive System Disorders (reported as AESI if ≥ 2, per CTCAE v. 5)[1]
1. Amenorrhea
2. Premature menopause / Primary ovarian insufficiency

[1] Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).

8.4. Treatment of Overdose

For this study, any dose of study treatment greater than 450 mg daily dose of study treatment within a 24-hour period will be considered an overdose.

In the event of an overdose, the investigator will:

1. Contact the medical monitor immediately (refer to Section 10.10.3 for contact information).
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 4 days.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

- Serial and trough PK samples will be collected during the study, as described in the SoA (Section 1.3) to inform development of a population PK model of nirogacestat. Refer to Table 11 for PK blood draw schedule. To minimize the amount of time a participant is required to remain onsite during a public health emergency such as COVID-19, the 3-hour C1D1 PK sample may be omitted with prior medical monitor / sponsor approval.
- Whole blood samples of approximately 4 mL each will be collected for measurement of serum concentrations of nirogacestat as specified in the SoA.
- The actual date and time (24-hour clock time) of each sample will be recorded.

- Instructions for the collection, handling, and shipment of pharmacokinetic samples will be in the central laboratory manual.
- Samples will be used to evaluate the PK of nirogacestat and associated metabolites.
- Genetic analyses will **not** be performed on these samples.
- Participant confidentiality will be maintained.
- Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Table 11 PK Blood Draw Schedule

Visit	Timepoint
Cycle 1 Day 1[3]	Serial PK[1] (pre-dose, 0.25-, 0.5-, 1-, 1.5-, 2-, and 3-hour post dose)
Cycle 1 Day 8[3]	Trough PK[2] (pre-dose)
Cycle 1 Day 15[3]	Trough PK[2] (pre-dose)
Cycle 1 Day 22[3]	Trough PK[2] (pre-dose)
Cycle 2 Day 28[3]	Trough PK[2] (pre-dose)
Cycle 4 Day 1 and Every 3 cycles	Trough PK[2] (pre-dose)

[1]Serial PK:
- Double-blind phase: required for all participants.
- OLE phase: required for participants who were previously randomized to placebo in the double-blind phase only.
- All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing will not be captured as protocol deviations if the exact time of the sample collection is noted on the source document and eCRF.

[2]Trough PK:
- Required for all participants.
- The evening before the study visit, participant will record the exact time study treatment was taken in the home ePRO device. Participant will not take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.

[3]OLE Cycle 1 and 2 PK assessment are not applicable for participants who were previously randomized to nirogacestat in the double-blind phase.

8.6. Pharmacodynamics

Optional blood and tumor samples will be collected for the evaluation of pharmacodynamic biomarkers (refer to Section 8.8).

8.7. Genetics

- A blood sample and tumor biopsy (archival sample may be used; Section 8.1.3) will be collected from all participants (unless prohibited by local regulations) prior to the first dose of study treatment to perform genotyping for germline and somatic mutation in APC and CTNNB1 genes to determine the frequency of these mutations in desmoid tumors. Response to study treatment based on mutational status may be evaluated.
- In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.
- Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual.
- Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last study visit at a facility selected by the sponsor to enable further analysis of biomarker responses to nirogacestat.
- Refer to Section 10.5 for information regarding genetic research.

8.8. Biomarkers

- Participation is optional for genetic research and those who do not wish to participate may still enroll in the study.
- The following optional tumor and blood samples for biomarker research will be collected from consenting participants only, as specified in the SoA (Section 1.3).
  - Before study treatment initiation samples:
    - Pharmacogenomic blood sample
    - Archival or fresh tumor tissue sample (Section 8.1.3)
  - After study treatment initiation sample:
    - Fresh tumor tissue sample
- Analyses may include the following: (1) expression analysis of genes and proteins associated with the Notch pathway, (2) molecular analysis of genomic alterations associated with Notch signaling (for example, Notch 1 mutations), (3) levels of NICD, (4) molecular profiling of tumor cells to identify potential markers of response/resistance to nirogacestat.
- Additional biomarkers may also be measured, based on emerging clinical and literature data pertaining to Notch biology. Full details regarding collection, processing, storage and shipping of all PD biomarker samples will be provided in the central laboratory manual.
- Samples may be tested for expression on Notch pathway genes to evaluate their association with the observed clinical responses (e.g., PFS or ORR) to study treatment.

- Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last study visit at a facility selected by the sponsor to enable further analysis of biomarker responses to nirogacestat.

8.8.1. RNA Transcriptome Research

Transcriptome studies may be conducted using microarray and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood and tumor sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to desmoid tumors or the action of nirogacestat.

The same samples may also be used to confirm findings by application of alternative technologies.

8.8.2. RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative reverse transcriptase polymerase chain reaction, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in an RNA expression profile for each blood and tumor sample. The RNAs assayed may be those involved with the pathogenesis of desmoid; the absorption, distribution, metabolism, or excretion of nirogacestat; or in the participant's response to nirogacestat. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to nirogacestat or the pathogenesis of desmoid. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to desmoid or the action of nirogacestat.

8.8.3. Proteome Research

Plasma and tumor proteome studies may be performed by 2-D gel separation, and/or peptide mass mapping, or an alternative equivalent procedure. Proprietary algorithms and standard statistical techniques, such as analysis of variance and analysis of covariance, may be used to identify individual proteins exhibiting statistically significantly different changes in their levels between samples and/or between groups of samples. These differentially expressed proteins will be identified by mass spectrometry or equivalent technology. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to desmoid and medically related conditions or the action of nirogacestat.

The samples may also be used to confirm findings by application of alternative technologies.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Nirogacestat treatment will increase the time to progression compared to placebo in participants with desmoid tumors.

The following hypothesis will be tested using a stratified log-rank test:

H0: PFS(t)placebo = PFS(t)nirogacestat

Ha: PFS(t)placebo < PFS(t) nirogacestat

where PFS(t) represents the progression free survivorship function at time, t

9.2. Sample Size Determination

The study sample size is based on the PFS endpoint. A total of 51 events will provide 90% power and a 1-sided type 1 error rate of 0.025 (1-side hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat group is 20 months and 8 months in the placebo group (corresponding to a hazard ratio of 0.4 relative to placebo). Assuming a 10% dropout rate and a 20% spontaneous regression rate, 118 participants will be randomized in a 1:1 ratio to observe the required number of events.

The assumptions selected for sample size estimate are based partially on the results reported in Gounder, 2018. As outlined in Section 2.2.3, a randomized double-blind Phase 3 study was conducted in desmoid participants comparing sorafenib to placebo. The study established a median PFS of 11.3 months for the placebo participants; but the population enrolled was a more heterogeneous desmoid population with only approximately 43% of the placebo participants having progressing tumors. The NIR-DT-301 study will only enroll progressing participants; therefore, a shorter median of 8 months PFS for placebo was used to calculate the sample size.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Intent-to-Treat (ITT)	The Intent-to-Treat (ITT) Population will consist of all participants who are enrolled and randomized to study treatment (nirogacestat or placebo). Participants will be analyzed according to the treatment they were randomized to and the strata to which they have been assigned. Participants who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

Population	Description
Per-Protocol Population	The Per-Protocol Population will be defined for supportive analysis and will consist of those participants who have no major protocol deviations, including mis-randomizations or mis-stratifications. Participants will be analyzed according to the study treatment actually received (i.e., at least 1 dose of the study treatment).
Safety	The Safety Population will consist of all participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Detailed methodology for summary and statistical analyses of the data collected in this study will be documented. In addition, strategies on dealing with protocol deviations due to COVID-19 will be detailed in the SAP. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary efficacy endpoint is PFS, which is defined as the time from randomization until the date of assessment of progression or death by any cause (whichever occurs first). Progression will be determined radiographically by independent, blinded Central Imaging Review using RECIST v1.1 (Eisenhauer, 2009) as described in Section 8.1.1 or clinically by an investigator whose assessment is qualified via independent blinded central clinical review as described in Section 8.1.2. Participants who have not progressed or died will be censored at the date of the last response assessment. Participants who do not have any response assessments will be censored at the date of randomization. Sensitivity analysis utilizing alternative censoring methods will be described in the SAP. The primary efficacy endpoint, PFS, will be analyzed using a 1-sided stratified log-rank test to compare the distributions between nirogacestat and placebo at a 1-sided alpha level of 0.025. The primary analysis of PFS will be performed on the ITT Population, defined as all participants who are randomized to study treatment after the

	required number of PFS events have been observed. Participants in the ITT Population will be analyzed in the study treatment arm to which they are randomized. Progression-free survival data will be summarized with Kaplan-Meier methodology. Two-sided 95% CIs for the median time-to-event in each study treatment arm, the event rates at specific time points, and the hazard rate ratio will be computed. There will be a Central Reader Agreement provided to Central Imaging Review and an Imaging Review Charter provided to the sponsor that will clearly detail the entire process.
Secondary	Secondary endpoints include: • Overall response rate, defined as the proportion of participants with CR + PR assessed via central reader using RECIST v1.1; • Change in tumor volume from baseline as assessed by MRI volumetric; • Change in PRO measures (GODDESS [symptom scale], BPI short form, PROMIS PF 10a short form plus 3 additional items from the PROMIS item banks, GODDESS [impact scale] and EORTC QLQ-C30) from baseline; and • Duration of response for participants whose best response is CR or PR. In order to preserve the total type I error for the study, secondary endpoints will be evaluated in a hierarchical fashion according to the order that will be outlined in the SAP. Testing will only be performed if the null hypothesis of the primary endpoint is rejected. Overall response rate will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. Duration of response will be calculated as the time from the first response until progression or the last date of response assessment and will be summarized descriptively. Change in tumor volume assessed by MRI will be analyzed using a repeated measures model adjusting for baseline tumor volume and randomization strata. The change from baseline in total score for PRO assessment endpoints listed above will be analyzed using a repeated measures mixed model adjusting for fixed and random factors. Total scores will be calculated according to the published guidance for each specific scale if available. In addition, the change from baseline in the QLQ-C30 questions regarding rating of overall health and overall quality of life will be compared between treatment groups. The

	total scores and sub-scores at each time-point will be summarized with descriptive statistics and displayed graphically. All data collected after crossover to nirogacestat (for participants who were previously randomized to placebo in the double-blind phase and receive nirogacestat in the OLE phase after radiographic disease progression) will be analyzed and reported separately.
Exploratory	Will be described in the SAP finalized before database lock.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Safety Endpoints	The safety and tolerability of nirogacestat will be evaluated by means of study treatment-related AE reports, physical examinations, and laboratory safety evaluations. Adverse events will be graded by the investigator according to the CTCAE v5.0 and coded using the Medical Dictionary for Regulatory Activities. The focus of AE summaries will be on Treatment Emergent AEs, those with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. Clinical laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and study visit. Descriptive statistics for the actual values (and/or change from baseline) or frequencies of clinical laboratory parameters over time. Incidence of abnormalities and shift tables will be presented.

9.4.3. Other Analyses

Sensitivity analyses, pharmacokinetic, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

9.5. Interim Analyses

One interim analysis may be performed after 26 PFS events (corresponding to approximately 50% of the total events) have been observed. Progression will be determined by independent, blinded Central Imaging Review determination for this analysis. A Lan-DeMets alpha-spending

function with an O'Brien-Fleming stopping boundary will be used for the interim analysis of PFS. The study may be stopped for overwhelming efficacy or futility.

At the interim analysis, the study may be stopped for futility if the observed hazard ratio is greater than 0.91 or stopped for overwhelming efficacy if the hazard ratio is less than or equal to 0.31 in favor of nirogacestat. This is equivalent to a Z-score greater than -0.252 for futility or less than -2.96 for efficacy. The alpha spent for the interim testing is 0.002 and the remaining 0.023 alpha will be allocated to the final analysis.

The analysis will be conducted by an independent committee consisting of at least 1 statistician. Results of the interim analysis will not be disseminated among investigators or anyone directly involved in study conduct.

The interim analysis plan will describe the planned interim analyses in greater detail.

9.5.1. Data Monitoring Committee

The study will utilize an independent data monitoring committee (DMC) and will operate according to an established Charter. The committee will be composed of approximately 3 to 4 members including physicians knowledgeable in the treatment of desmoid tumors and an independent statistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data. Sponsor employees will not be voting members of the DMC. The DMC will be responsible for ongoing monitoring of the unblinded safety and benefit/risk profile of participants in the study. Reviews will include aggregate safety, targeted medical events of special interest, serious AE data and aggregate endpoint data.

Following each data review, the DMC may recommend 1) no changes to the study are needed, 2) changes to the protocol or informed consent based on clinical safety findings, or 3) early termination of the study based on safety analyses. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the sponsor for final decision. Additionally, the DMC may be asked to assist the sponsor in evaluating the impact of data from other company-sponsored studies or other published studies.

The DMC Charter will outline the frequency of meetings and detail all aspects of DMC's scope of review and procedures.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines; and
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board/independent ethics committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of serious adverse event or other significant safety findings as required by IRB/IEC procedures; and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form (ICF).
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study as required by the IRB/IEC.
- Consent is required for the collection of pharmacogenomic samples (blood and tumor biopsies).
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

The study will utilize an independent data monitoring committee (DMC) and will operate according to an established Charter (Section 9.5.1). In addition, a steering committee will be established to support the development of nirogacestat for the treatment of desmoid tumor/aggressive fibromatosis. The purpose and provisions of the DMC will be specified in the DMC Charter.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be entered into the electronic case report forms (eCRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be indicated in the monitoring plan to ensure the protocol and GCP is followed.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator according to specifications in the ICH guidelines, local regulations, or as specified in the clinical trial agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Investigators will maintain records separate from the eCRFs in the form of clinical charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the participant signed informed consent prior to participation in the study. Source documents must completely reflect the nature and extent of the participant's medical care and must be available for source document verification against entries in the eCRFs when the sponsor's monitor visits the site. In order to meet data integrity requirements, source documentation should be attributable, legible, contemporaneous, accurate, available/accessible, original, complete and credible. All information obtained from these documents will be kept in strict confidentiality. Definition of what constitutes source data can be found in the study reference manual.

10.1.8. Study and Site Closure

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Study-site closure prior to completion of the study should be avoided. The investigator and sponsor will agree to the circumstances that could cause early study-site closure.

Conditions that may warrant early study-site closure or study termination may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to participants participating in the study;
- A negative change in the risk/benefit assessment;
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator; or
- The decision on the part of the sponsor to suspend or discontinue nirogacestat development.

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study treatment pertaining to the study must be returned to the sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the participants and assure appropriate therapy and follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment (nirogacestat or placebo) administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the electronic case report form. In the event of a public health emergency, clinical laboratory assessments may be performed locally with results and local laboratory normal values entered into the eCRF.
- Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5 and Sections 6.7.2 and 6.7.3 protocol.
- Additional tests, as part of unscheduled visits, may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing (urine or serum as described in the SoA; Section 1.3) will be conducted at monthly intervals during the double-blind and OLE study treatment phases.
- Urine pregnancy testing (will be conducted at monthly intervals during the double-blind and OLE study treatment phases for women of child-bearing potential. Refer to Section 8.2.6 for more details on the monthly pregnancy testing requirements.
- Serum pregnancy tests may be conducted in place of urine pregnancy tests throughout the study if required by local regulations.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Investigators must document their review of each laboratory safety report.

Table 12 Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry[2]	Urinalysis	Serology[5]	Hormone Levels[6]

• HGB
• HCT
• PLT count
• RBC count
• RBC Indices:
  o MCV
  o MCH
• % Reticulocytes
• WBCC with Differential[1]:
  o neutrophils
  o lymphocytes
  o monocytes
  o eosinophils
  o basophils
	• AST/SGOT
	• ALT/SGPT
	• D-BIL
	• TBIL
	• GGT
	• Sodium
	• Chloride
	• Potassium
	• Bicarbonate
	• Inorganic phosphorus
	• Alkaline phosphatase
	• Creatinine[3]
	• Estimated glomerular filtration rate
	• BUN
	• Glucose (non-fasting)
	• Uric acid
	• Albumin
	• Total protein
		• Specific gravity
		• Bilirubin
		• Glucose
		• Leukocyte esterase
		• Nitrite
		• Protein
		• Urobilinogen
		• Blood
		• Ketones
		• pH
		• Microscopy[4]
			• HIV antibody
			• HBV
			  o HBsAg
			• HCV
			  o hepatitis C antibody (HCV PCR if hepatitis C antibody positive)
				Females:
				• TSH[7]
				• Prolactin[7]
				• AMH
				• LH
				• FSH
				• Estradiol
				• Progesterone
				
				Males:
				• Total testosterone
				• Free testosterone
				• Progesterone
				• FSH
				• LH

ALT = alanine aminotransferase; AMH = anti-müllerian hormone; AST = aspartate aminotransferase; BUN = blood urea nitrogen; D-BIL = direct bilirubin; FSH = follicle stimulating hormone; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCT = hematocrit; HCV = hepatitis C virus; HGB = hemoglobin; HIV = human immunodeficiency virus; LH = luteinizing hormone; MCH = mean cell hemoglobin; MCV = mean cell volume; PCR = polymerase chain reaction; PLT = platelet; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT =serum glutamic-pyruvic transaminase; TBIL = total bilirubin; TSH = thyroid stimulating hormone; WBCC = white blood cell count

1) Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.
2) Details of liver stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Sections 7.1.1 and 10.6.
3) If creatinine > 1.5 × ULN then calculated creatinine clearance must be ≥ 60 mL/min (using the Cockcroft-Gault formula).
4) Microscopy examination is performed only if blood or protein is abnormal.
5) Serology only required at screening.

Hematology	**Chemistry[2]**	**Urinalysis**	**Serology[5]**	**Hormone Levels[6]**
6) Hormone level assessments for both females and males are required per the SoA in Section 1.3. Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment). 7) Female hormone levels for TSH and prolactin are only required at Screening and EOT.				

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Event (AE)

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events <u>Meeting</u> the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, hormone levels, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE or serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. 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 AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include 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.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- All required information pertaining to the AE/SAE will be recorded in the electronic case report form (eCRF). SAEs will require additional information to be reported to Safety utilizing a paper SAE form that must be scanned and emailed or faxed to Safety immediately, without undue delay, under no circumstances later than 24 hours after becoming aware of the event (refer to Section 10.3.4 for further SAE reporting details).
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Safety in lieu of completion of the SAE eCRF page/paper SAE form.
- There may be instances when copies of medical records for certain cases are requested by Safety for reported SAEs. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of all SAEs/AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For those SAEs/AEs not listed in the CTCAE, the following grading system will be used:

- CTCAE **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- CTCAE **Grade 2** Moderate; minimal, local or noninvasive treatment indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- CTCAE **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- CTCAE **Grade 4** Life-threatening consequences; urgent treatment indicated.
- CTCAE **Grade 5** Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (Section 10.3.2), **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment (nirogacestat or placebo) and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure, when making an assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Safety. However, **it is very important that the investigator always make an assessment of causality for every event with the initial SAE reporting to Safety via paper SAE form.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Safety with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF. In addition, sites must email [redacted] or fax a follow-up SAE form to Safety.
- The investigator will submit any updated SAE data to Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Safety

- The primary mechanism for reporting an SAE will be by emailing (preferred method) to Safety at PV@springworkstx.com or faxing the paper SAE form.
- A copy of the paper SAE form can be found in the investigator site file.
- All SAEs must be reported to Safety immediately, without undue delay, under no circumstances later than 24 hours after awareness. This initial reporting can be done by emailing/faxing the SAE form to Safety, or by entering the SAE term into the electronic case report form (eCRF) which will alert Safety of the event. However, a paper SAE form must still be completed and submitted to Safety as soon as possible.

- In rare circumstances in the absence of email or facsimile equipment, notification by telephone is acceptable with a copy of the SAE form sent by overnight mail or courier service. However, initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.
- After the study is completed at a given site, the eCRF system will be locked to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the eCRFs have been locked, then the site can report this information on a paper SAE form to the Safety by telephone/email/fax.
- Contacts for SAE reporting can be found in Section 10.10.4.

10.3.5. Definition of AR, SAR and SUSAR

Adverse Reaction (AR):
An AR is any noxious and unintended response to a medical product or procedure, for which a causal relationship with the product or procedure is at least a reasonable possibility (i.e., the relationship cannot be ruled out).
Serious Adverse Reaction (SAR):
A SAR is an SAE for which a causal relationship with the product or procedure is at least a reasonable possibility (i.e., the relationship cannot be ruled out).
Suspected Unexpected Serious Adverse Reaction (SUSAR):
A SUSAR is a SAR that is judged as unexpected. An event is considered “unexpected” if it is not listed as expected in the reference safety information (RSI) section of the investigator brochure (IB) or summary of product characteristics.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Women of Childbearing Potential (WOCBP) is defined as a woman that is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment (nirogacestat or placebo), additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy; or
   - Documented bilateral salpingectomy; or
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry. Bilateral tubal occlusion is not considered to be a permanent form of infertility.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.* • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion • Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.* • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o Oral o Intravaginal o Transdermal o Injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable • Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) Barrier methods such as condoms (male or female) or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream or vaginal suppository must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information:

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

10.5. Appendix 5: Genetics

Use and analysis of deoxyribonucleic acid (DNA):

- Genetic variation may impact a participant's response to study treatment (nirogacestat or placebo), susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and institutional research boards/independent ethic committees allow, DNA analysis will be collected from participant's blood sample (referred to as the optional pharmacogenetic blood sample in the SoA [Section 1.3.1]) and participant's tumor biopsy required for disease confirmation at baseline if archival tissue not available, and optional tumor biopsy at the EOT visit will be collected from consenting participants.
- DNA samples will be used for research related to nirogacestat or desmoid and related diseases. They may also be used to develop tests / assays including diagnostic tests related to nirogacestat or treatments of this drug class and desmoid. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analyzed for the presence of known mutations. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to nirogacestat or study treatments of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on nirogacestat continues but no longer than 10 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥ 4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (> 35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR > 1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study treatment (nirogacestat or placebo) • Report the event to the sponsor **within 24 hours** • Complete the liver event in the eCRF and complete the SAE eCRF form if the event also met the criteria for an SAE[2] • Perform liver chemistry follow-up assessments • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) • Restart/rechallenge is **not allowed per protocol and not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments**MONITORING:** **If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR > 1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR)	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF page • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF page.

and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT ≥ 3xULN AND bilirubin < 2xULN and INR ≤ 1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• Record alcohol use on the liver event alcohol intake eCRF **ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; eCRF = electronic case report form; HPLC = high performance liquid chromatography; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; SAE = serious adverse event; ULN = upper limit of normal;

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (> 35% direct bilirubin) or ALT ≥ 3xULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

Liver Chemistry Increased Monitoring Criteria with Continued Study Treatment

Liver Chemistry Increased Monitoring Criterion and Follow-Up	
Criterion	**Actions**
ALT ≥ 3xULN and < 5xULN **and** bilirubin < 2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the medical monitor within **24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1. • If, after 4 weeks of monitoring, ALT < 3xULN and bilirubin < 2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

10.7. Appendix 7: Eastern Cooperative Oncology Group Performance

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655

10.8. Appendix 8: RECIST (Response Evaluation Criteria in Solid Tumors) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours:

Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

Categorizing lesions at Baseline:

- Only participants with measurable disease (i.e., at least one measurable lesion) at screening are included.

Measurable lesion – Lesion that can be accurately measured in at least one dimension (longest diameter [LD]) in the plane of measurement is to be recorded) and with longest diameter at least twice the slice thickness and at least 10 mm when assessed by computed tomography (CT) or magnetic resonance imaging (MRI)

- Measurable disease will be assessed by CT or MRI.
- The same method of assessment (CT or MRI) and the same technique will be used to characterize each identified and reported lesion at screening and during follow-up.
- Target Lesion - The investigator will select up to 5 target lesions in total, representative of all involved organs at Baseline.
- Non-target Lesion--All other lesions (or sites of disease) will be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Methods of Measurement

CT or MRI must be used to measure target lesions selected for response assessment. Conventional CT and MRI will be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Recording Tumor Assessments

All sites of disease must be assessed at screening. Screening assessment must be done within 28 days of starting study treatment (nirogacestat or placebo). For an adequate screening assessment, all required scans must be done within 28 days prior to first dose of study treatment and all disease must be documented appropriately. Participants must have progressive disease (PD) within a 12-month period prior to the screening visit scan.

At follow-up, disease site must be assessed using the method (CT or MRI) and same technique as screening, including consistent administration of contrast (CT only) and timing of scanning. If a change needs to be made the case must be discussed with the sponsor.

Unequivocal new lesions will be recorded at follow-up time points. Measurement of new lesions is not required. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Response Criteria:

Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of LD recorded since the treatment started or the appearance of one or more unequivocal new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the start of study treatment). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria (defined below).

Time point response: patients with target disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Participants with a global deterioration of health status requiring discontinuation of study treatment without objective evidence of disease progression at that time will be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Confirmation

- **Confirmation of progression:** assessment of PD will be confirmed and documented by Central Imaging Review (an independent, blinded central radiological review committee).
- **Confirmation of response:**
  - The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
  - To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met.
- **Confirmation of SD:** in the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD

is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
    - The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specifies the minimal time interval required between two measurements for determination of SD. This time interval should consider the expected clinical benefit that such a status may bring to the population under study.

10.9. Appendix 9: Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ADL	Activities of daily living
ALT	Alanine aminotransferase
AMH	Anti-müllerian hormone
APC	Adenomatous polyposis coli
AR	Adverse reaction
AST	Aspartate aminotransferase
BID	Twice daily
BPI	Brief pain inventory
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
CI	Confidence interval
ConMed	Concomitant medication
CPK	Creatine phosphokinase
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTNNB1	β-catenin
CYP3A4	Cytochrome P450 3A4
D-BIL	Direct bilirubin
DDI	Drug-drug interaction
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid,
DT/AF	Desmoid tumors/aggressive fibromatosis
DTP	Direct to participant
DTRF	Desmoid Tumor Research Foundation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event free survival
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOT	End of treatment
ePRO	Electronic patient report outcome
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin embedded
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice

Abbreviation	Definition
GGT	Gamma-glutamyl transferase;
GODDESS	GOunder/DTRF DEsmoid Symptom/Impact Scale
GS	Gamma-secretase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
Hes1	Hairy and enhancer of split-1
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
I/E	Inclusion/exclusion
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
LD	Longest diameter
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
MCH	Mean cell hemoglobin
MCV	Mean cell volume
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MSK/DTRF DTIS	Memorial Sloan Kettering/Desmoid Tumor Research Foundation Desmoid Tumor Impact Scale
MSK/DTRF DTSS	Memorial Sloan Kettering/Desmoid Tumor Research Foundation Desmoid Tumor Symptom Scale
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NICD	Notch intracellular domain
NIR	nirogacestat
NSAIDs	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PGIC	Patient global impression of change

Abbreviation	Definition
PGIS	Patient global impression of severity
PK	Pharmacokinetic
PLT	Platelet
POI	Primary ovarian insufficiency
PopPK	Population pharmacokinetic
PR	Partial response
PRO	Patient-reported outcome
PROMIS PF	Patient-Reported Outcomes Measurement Information System Physical Function
QoL	Quality of life
QT	Uncorrected QT interval
QTcF	Corrected QT interval by Fridericia
QRS	QRS Complex
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of activities
STSs	Soft-tissue sarcomas
SUSAR	Suspected unexpected serious adverse reaction
TdP	Torsades de Pointes
TBIL	Total bilirubin
TKI	Tyrosine kinase inhibitors
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
v	Version
WBCC	White blood cell count
WOCBP	Women of childbearing potential

10.10. Appendix 10: List of Contacts for Study

10.10.1. Sponsor

SpringWorks Therapeutics
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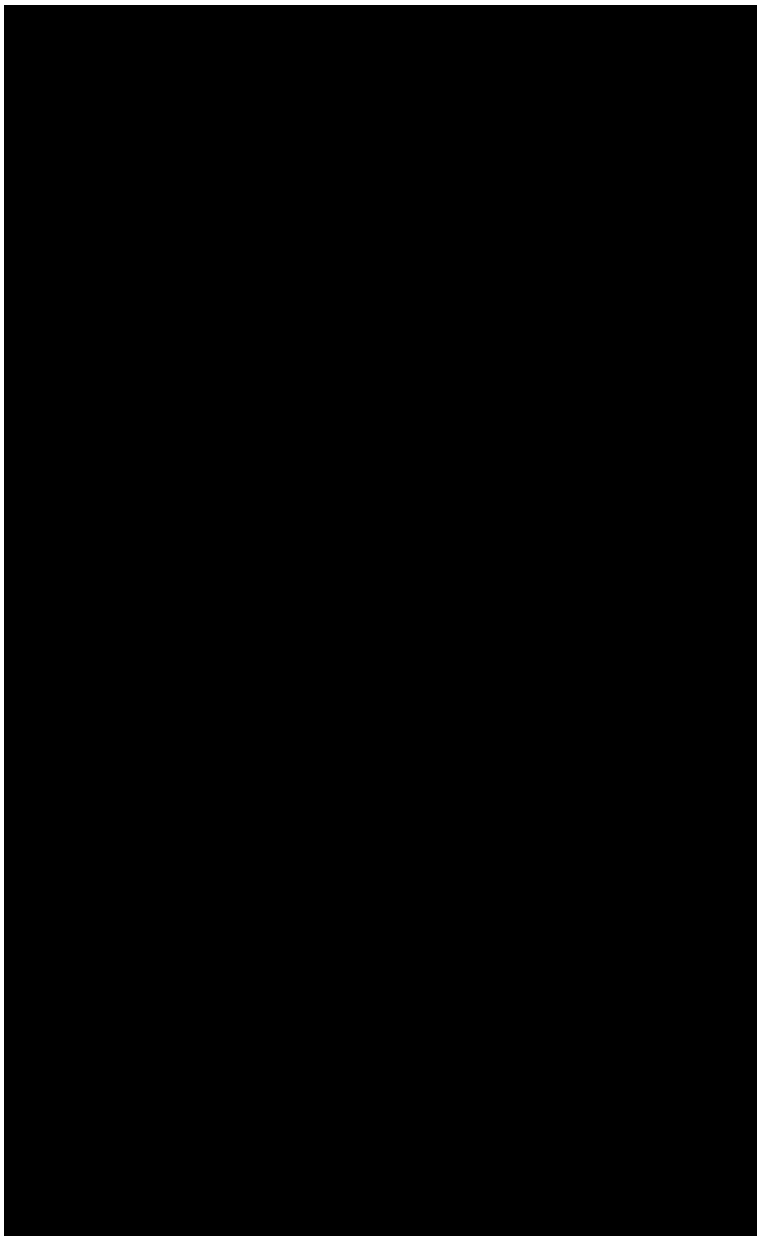

11. REFERENCES

Bo N, Wang D, et al. Analysis of β-catenin expression and exon 3 mutations in pediatric sporadic aggressive fibromatosis. Pediatr Dev Pathol. 2012 May Jun;15(3):173-8.

Casali PG, Abecassis N, et al.; ESMO Guidelines Committee and EURACAN. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; Epub ahead of print, May 28.

de Camargo VP, Keohan ML, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). Cancer. 2010 May 1;116(9):2258-65.

Eisenhaur EA, Therasse P, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Gounder, M., Mahoney M, et al. Phase III, randomized, double-blind, placebo-controlled trial of sorafenib in desmoid tumors J Clin Oncol 36, 2018 (suppl; abstr 11500).

Hosalkar, H, Fox EJ, et al. Desmoid Tumors and Current Status of Management. Orthop Clin N Am 2006(37):53-63.

Janinis J, Patriki M, et al. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol. 2003 Feb;14(2):181-90.

Kasper B, Baumgarten C, et al.; Desmoid Working Group. Management of sporadic desmoid type fibromatosis: a European consensus approach based on patients' and professionals' expertise- a sarcoma patients EuroNet and European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative. Eur J Cancer. 2015 Jan;51(2):127 36.

Kasper B, Gruenwald V, et al. Imatinib induces sustained progression arrest in RECIST progressive desmoid tumours: Final results of a phase II study of the German Interdisciplinary Sarcoma Group (GISG). Eur J Cancer. 2017 May; 76:60-67.

Kasper B, Ströbel P, et al. Desmoid tumors: clinical features and treatment options for advanced disease. Oncologist. 2011;16(5):682-93.

Klinakis A, Szabolcs M, et al. Myc is a Notch1 transcriptional target and a requisite for Notch1-induced mammary tumorigenesis in mice. Proc Natl Acad Sci USA. 2006 Jun 13;103(24):9262-67.

Kummar S, O'Sullivan Coyne G, et al. Clinical activity of the γ-secretase inhibitor PF-03084014 in adults with desmoid tumors (Aggressive Fibromatosis). J Clin Oncol. 2017 May 10;35(14):1561-69.

Lazar AJ, Tuvin D, et al. Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol. 2008 Nov;173(5):1518-27.

Lewis JJ, Boland PJ, et al. The enigma of desmoid tumors. Ann Surg. 1999 Jun;229(6):866-72.

Messersmith WA, Shapiro GI, et al. A Phase I, dose finding study in patients with advanced solid malignancies of the oral γ-secretase inhibitor PF-03084014. Clin Cancer Res. 2015 Jan 1;21(1):60-7.

Penel N, Le Cesne A, et al. Surgical versus non-surgical approach in primary desmoid-type fibromatosis patients: A nationwide prospective cohort from the French Sarcoma Group. Eur J Cancer. 2017 Sep; 83:125-31.

Quintini C, Ward G, et al. Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg. 2012 Mar;255(3):511-6.

Rampazzo E, Persano L, et al. Wnt activation promotes neuronal differentiation of glioblastoma. Cell Death Dis. 2013 Feb 21;4: e500.

Rodilla V, Villanueva A, et al. Jagged1 is the pathological link between Wnt and Notch pathways in colorectal cancer. Proc Natl Acad Sci USA. 2009 Apr 14;106(15):6315-20.

Schöffski P, Requilé A, et al. Assessment of physician's systemic treatment preferences for patients with advanced desmoid-type fibromatosis: experience-based medicine in the absence of high-level evidence. Oncol Res Treat. 2018;41(4):214-19.

Shang H, Braggio D, et al. Targeting the Notch pathway: a potential therapeutic approach for desmoid tumors. Cancer. 2015 Nov 15;121(22):4088-96.

Sharma VM, Calvo JA, et al. Notch1 contributes to mouse T cell leukemia by directly inducing the expression of c-myc. Mol Cell Biol. 2006 Nov;26(21):8022-31.

Skubitz KM. Biology and Treatment of aggressive fibromatosis or desmoid tumor. Mayo Clin Proc. 2017 Jun;92(6):947-64.

Smith AJ, Lewis JJ, et al. Surgical management of intra-abdominal desmoid tumours. Br J Surg. 2000 May;87(5):608-13.

Tejpar S, Nollet F, et al. Predominance of beta-catenin mutations and beta-catenin dysregulation in sporadic aggressive fibromatosis (desmoid tumor). Oncogene. 1999 Nov 11;18(47):6615-20.

Ungerbäck J, Elander N, et al. The Notch-2 gene is regulated by Wnt signaling in cultured colorectal cancer cells. PLoS One. 2011 Mar 18;6(3): e17957.

Villalobos VM, Hall F, et al. Long-term follow-up of desmoid fibromatosis treated with PF-03084014, an oral gamma secretase inhibitor. Ann Surg Oncol. 2018 Mar;25(3):768-75.

The protocol amendment summary of changes for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (27 November 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Rationale for the Amendment:

ADMINISTRATIVE AND OTHER		
Section # and Name	**Description of Change**	**Brief Rationale**
Title Page	DeFi added as study acronym.	Study acronym name added.
1.3.1 Double-Blind Phase SoA; 1.3.2 Open-Label Extension Phase SoA;	Clarifications for the footnotes added within the SoA table: -Physical examination described as "complete" or "brief" -12-lead ECG timing described as "pre-& post dose" -PK sampling timing described as "serial" or "trough"	Clarifications added.
5.4. Screen Failures; 6.3.1. Randomization;	How the participant number will be assigned at the screening visit changed from the interactive response technology (IRT) to the laboratory requisition form.	Corrected error on how participant number will be assigned.
6.6. Dose Modification	Updated the following language (changed "should" to "will"): *"Every effort <u>will</u> be made to administer study treatment at 150 mg BID..."* *"Interruption of study treatment will continue until*	To clarify the expectation of this assessments as a requirement versus a recommendation.

	the toxicity is resolved to ≤Grade 1 or baseline."	
7.1.2. QTc Stopping Criteria	Updated the following language (changed "should" to "must"): *"Any new clinically relevant finding must be reported as an AE."*	To clarify the expectation of this assessments as a requirement versus a recommendation.
7.3. Lost to Follow up	Updated the following language (changed "should" to "must"): *"These contact attempts must be documented in the participant's medical record."*	To clarify the expectation of this assessments as a requirement versus a recommendation.
8.2.1. Demographics Data and Medical History	Updated the following language (changed "review" to "collection"): *"...and collection of concomitant medications."*	To provide clarification.
8.2.2. Physical Examinations and Eastern Cooperative Oncology Group Performance status	Updated the following language (changed "should" to "must": *"Investigators must pay special attention to clinical signs related to previous serious illness, and changes from baseline will be recorded in the source documentation."* *"New or worsened clinically significant abnormalities must be recoded as AEs on the eCRF page."*	To clarify the expectation of this assessments as a requirement versus a recommendation.
6.3.1. Randomization;	Updated the following language (changed "should" to "must"): *"The tumor location used for stratification must be the same as the reported target*	To clarify the expectation of this assessments as a requirement versus a recommendation.

	lesion used for assessment of the primary endpoint."	
8.4. Treatment of Overdose	Updated the following language (changed "should" to "will"): *"In the event of an overdose, the investigator <u>will</u>…"*	To clarify the expectation of this assessments as a requirement versus a recommendation.
10.1.5. Committees Structure	Section added describing the DMC and steering committees.	Inadvertently omitted.
10.3.3. Recording and Follow-Up of AE and/or SAE	Updated the following language (changed "should" to "will"): *"The intensity of all SAE/AEs <u>will</u> be graded according to the Common Terminology Criteria…"* "*For those SAEs/AEs not listed in the CTCAE, the following grading system <u>will</u> be used.*"	To clarify the expectation of this assessments as a requirement versus a recommendation.
11. References	New abbreviations added.	New abbreviations added.
PATIENT-REPORTED OUTCOMES (PROs)		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1. Synopsis; 1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; 3. Objectives and Endpoints; 8.1.2.1. MSK/DTRF DTSS and MSK/DTRF DTIS; 9.4.1. Efficacy Analyses	PRO name updated for the Memorial Sloan Kettering/Desmoid Tumor Research Foundation Desmoid Tumor Symptom Scale and Desmoid Impact Scale (MSK/DTRF DTSS and DTIS).	Updated official names for these PRO assessments.
1.1. Synopsis; 1.3.1. Double-Blind Phase SoA;	MD Anderson Symptom Inventory (MDASI) removed.	The MDASI was replaced with the EROTC because it more accurately captures

1.3.2. Open-Label Extension Phase SoA; 3. Objectives and Endpoints; 8.1.2.7. MD Anderson Symptom Inventory		concepts important to desmoid patients.
1.1. Synopsis; 1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; 3. Objectives and Endpoints; 8.1.2.3. PROMIS PF Short Form 10a Plus 3 Additional Items from PROMIS Item Banks; 9.4.1. Efficacy Analyses	Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks added.	The PROMIS PF and the 3 additional questions were added to supplement the DTIS as this tool does not contain a "not applicable" field.
1.1. Synopsis; 1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; 3. Objectives and Endpoints; 8.1.2.4. EORTC-QLC-C30; 9.4.1. Efficacy Analyses	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30 added.	The EORTC replaced the MDASI as it more accurately captures key concepts that may be relevant to the desmoid patient population and includes 2 items asking about "general health" and "general quality of life," which will capture the patients' overall health related quality of life (HRQoL).
1.3.1. Double-Blind Phase SoA; 8. Study Assessments and Procedures	Home ePRO device training added to Schedule of Activities (SoA) table as a screening assessment.	Inadvertently omitted from the SoA table.
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA;	PRO assessment timepoints in the SoA table updated to refer directly to Table 8 and Table 9 for the double-blind and OLE PRO assessment administration schedules, respectively.	To eliminate the PRO assessment details in the SoA table and instead refer Section 8.1.2, Table 8 and Table 9.

	Footnote describing the PRO assessment details removed and language added referring the reader to Section 8.1.2, Table 8 and Table 9 for details.	
8.1.2. Patient Reported Outcomes	Details regarding the PRO assessment requirements were moved from the SoA table footnotes to this section. Table 8 and Table 9 were added to describe in detail the PRO assessment administration schedule for the double-blind and the OLE phases.	To avoid duplication between this section and the SoA table. To provide the reader with detailed requirements for the PRO assessments throughout the study.
8.1.2.2. BPI	The BPI numeric rating scale (NRS) updated from 0-11 to 0-10.	Corrected error.
8.1.2.5. PGIS; 8.1.2.6 PGIC	Clarification around the 7-day recall period for the PGIS and PGIC was added.	Inadvertently omitted.
STUDY TREATMENT		
Section # and Name	**Description of Change**	**Brief Rationale**
Beginning of each section throughout.	Study treatment defined as nirogacestat or placebo.	To clarify the definition of study treatment throughout.
6.1. Study Treatment(s) Administered;	Clarification added describing that all missed doses will be recorded in the home ePRO device. Details added describing the action to be taken if a participant misses a scheduled dose, if participant vomits any time after taking a dose, or inadvertently takes an extra dose of study treatment.	Further clarification on dosing administration instructions added.
6.1.2. Open-Label Phase Dosing Administration	More specific details added to describe how all double-blind	To clarify the requirements prior to entering the OLE

	EOT assessment must be completed in a blinded manner prior to unblinding the treatment assignment before the participant can enter the OLE phase.	phase with regard to treatment administration.
6.2. Preparation/Handling/ Storage/Accountability	Study treatment handling instructions added describing that "participants will be instructed to keep their study treatment in the bottles provided and not transfer it to any other containers."	Study treatment handling instructed added for clarity.
6.3.1. Randomization	Reference to unscheduled visits and how they may be necessary if study treatment is damaged/lost or a dose modification is required.	Updated for clarity.
7.1. Discontinuation of Study Treatment	Follow-up visit window updated from 30-45 days after last dose of study treatment to 30 days (+7 days).	Error corrected.
7.1. Discontinuation of Study Treatment	The following additional reason for discontinuation of study treatment early added: "Participant's study treatment is unblinded for safety reason."	Inadvertently omitted.
INCLUSION / EXCLUSTION CRITERIA		
Section # and Name	**Description of Change**	**Brief Rationale**
5.1. Inclusion Criteria #6; 5.2. Exclusion Criteria #11; 6.5.1.2. Excluded Concomitant Medications and/or Procedures;	Clarified the timeframe around participants who are receiving Nonsteroidal anti-inflammatory drugs (NSAIDs) as treatment for conditions other than desmoid tumor/aggressive fibromatosis (DT/AF) must be receiving them prior to the observed progression (inclusion criteria 2 and not	Revised to account for the potential treatment effect of NSAIDs if administered after the observed progression (inclusion criteria 2).

	within 28 days (changed from 14 days) of first dose of study treatment.	
5.2. Exclusion Criteria #8; 6.5.1.2. Excluded Concomitant Medications and/or Procedures;	Clarified the timeframe around participants who are currently using or anticipate using tyrosine kinase inhibitors (TKIs) not to be taking them after the observed progression (inclusion 2).	Revised to account for the potential treatment effect of TKIs if administered after the observed progression (inclusion criteria 2).
5.1. Inclusion Criteria #8; 10.2. Appendix 2: Clinical Laboratory Test	Serum creatinine clearance requirement changed from "should" to "must" be $\geq$60 mL/min/1.73 m^2.	To clarify the expectation of this assessments as a requirement versus a recommendation.
STUDY VISITS AND TIMING OF ASSESSMENTS		
Section # and Name	**Description of Change**	**Brief Rationale**
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA;	The Cycle 2 Day 1 study visit (week 5 / calendar day 29) was changed to Cycle 2 Day 28 (week 8 / calendar day 56) for the double-blind and OLE phases.	To allow for assessments to be collected at week 8 timepoint.
1.3.1. Double-Blind Phase SoA; 8. Study Assessments and Procedures	A minimum 21-day screening visit window added to footnote 1.	Clarification added to allow for a 1 week between the start of the screening and baseline PRO assessments.
1.2. Schema; 1.3.2. Open-Label Extension Phase SoA; 4.1.2. Overall Design for the Optional OLE Phase	Reason for study discontinuation updated to add "participant qualifies for Sponsor's Continued Access Plan."	To allow for those participants who may not have the option of continuing to commercially available nirogacestat at the close of the OLE phase of the study.
1.3.2. Open-Label Extension Phase SoA	*"Same as double-blind EOT"* language added to the OLE assessments that will be conducted as part of the double-blind EOT visit.	Visually aids in clarification of which OLE assessments are the same as the double-blind EOT visit assessments.
4.1.1. Overall Design for the Double-Blind Phase;	More detail added to the overall design for the double-	Details added for clarification.

4.1.2. Overall Design for the Optional OLE Phase	blind and OLE phase with regards to required study visits.	
8. Study Assessments and Procedures	Table 6 and Table 7 reorganized, duplicate information deleted that was already included in the SoA table and additional details added that were not found in the SoA table.	To provide additional instruction and avoid duplicate information contained within the SoA tables.
LABORATORY ASSESSMENTS		
Section # and Name	**Description of Change**	**Brief Rationale**
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; 8. Study Assessments and Procedures; 8.2.6. Pregnancy Testing; 10.2. Appendix 2: Clinical Laboratory Tests	The requirement for woman of childbearing potential (WOCBP) to self-administer monthly home urine pregnancy tests (in between study visits) was changed to require participants to return to the site or visit a sponsor approved local laboratory instead.	To ensure participant compliance with the urine pregnancy test requirements in between study visits.
8. Study Assessments and Procedures	The approximate amount of blood required from each participant increased from 133 mL each year for the double-blind and OLE phase, to 169 mL each year for the double-blind phase and 136 mL each year for the OLE phase.	The estimated amount of blood required per participant increased due to the addition of the trough PK sampling throughout the double-blind and OLE phases.
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; 8. Study Assessments and Procedures	In addition to the Cycle 1 Day 8 study visit, trough PK sampling was added to the following study visits: Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 28, Cycle 4 Day 1, and then every 3 cycles thereafter in both the double-blind and OLE phases.	To collect additional PK data for population PK and dose response analysis.

8.5. Pharmacokinetics	Table 10 describing the PK blood draw schedule added.	To provide a visualization of the PK blood draw schedule for the reader.
STATISTICAL ANALYSIS / RANDOMIZATION / BLINDING / DMC		
Section # and Name	**Description of Change**	**Brief Rationale**
4.1. Overall Design; 6.3.1. Randomization;	Stratification by primary tumor location changed from "favorable" versus "unfavorable" to "intra-abdominal" versus "extra-abdominal."	Categorizing the primary tumor locations as intra-abdominal (including mesentery and pelvis) or extra-abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations) more accurately reflects the way these tumors are described in clinical practice.
6.3.2.1. Breaking the Blind	Situations where breaking the blind would be acceptable was further detailed and broken out into 3 distinct categories: emergency situations, confirmed progressive disease, and all required number of progression free survival (PFS) events have been observed.	For further clarify the 3 different categories where breaking the blind would be acceptable in the study.
9.4.1. Efficacy Analyses	The following language was added to the primary endpoint: *"Participants who have not progressed or died will be censored at the date of the last response assessment. Participants who do not have any response assessments will be censored at the date of randomization. Sensitivity analysis utilizing alternative censoring methods will be described in the SAP."*	To specify censoring criteria for PFS.

9.4.1. Efficacy Analyses	The following language was added to the secondary endpoint: *"Duration of response will be calculated as the time from the first response until progression or the last date of response assessment and will be summarized descriptively."*	To clarify how the duration of response will be calculated and summarized.
9.4.1. Efficacy Analyses	Scoring details added for the PROMIS QLC-C30 and EORTC. MDASI scoring details removed.	Scoring details updated for additional PROs.
9.5.1. Data Monitoring Committee	Language describing that the DMC will be responsible for ongoing monitoring of the unblinded (changed from blinded) safety data and benefit/risk profile of participants in the study. Efficacy language removed from the DMC ongoing monitoring.	Error corrected.
ADVERSE EVENTS / SERIOUS ADVERSE EVENTS		
Section # and Name	**Description of Change**	**Brief Rationale**
8.3.1. Time Period and Frequency for Collecting AE and SAE Information	Language updated to require all medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as AEs and not on the medical history page.	Clarification added.
8.3.1. Time Period and Frequency for Collecting AE and SAE Information; 8.3.3. Follow-up of AEs and SAEs; 8.3.5. Pregnancy;	SAE and pregnancy reporting process updated to reflect that the primary method for reporting SAEs and pregnancies has changed from electronic reporting to paper reporting.	SAE and pregnancy reporting process updated.

10.3.3. Reporting and Follow-Up of AE and/or SAE; 10.3.4. Reporting of SAEs		

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Protocol: NIR-DT-301

Amendment 2 Summary and Rationale

Date of Amendment: 14 October 2019

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Apart from minor edits, formatting changes and necessary editorial updates, the following changes were made to the protocol amendment 1 (27Nov2018):

Rationale for the Amendment:

SUBSTANTIAL CHANGES		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1. Synopsis; 4.1. Overall Design; and 9.2. Sample Size Determination.	Sample size increased from 105 to 135 screened participants and from 94 to 118 randomized participants. In Section 9.2, the following language was added (see bold font below): *"Assuming a 10% dropout rate* ***and an additional 20% spontaneous regression rate****,* ***118*** ~~***94***~~ *participants will be randomized in a 1:1 ratio to observe the required number of events."*	Desmoid tumors can spontaneously regress and the increase in sample size was made to account for a projected spontaneous regression rate of 20%.
1.3.1. Double-Blind Phase SoA; 5.1. Inclusion Criteria; and 8.1.3. Tumor Biopsy.	The following language was revised in the SoA table (see bold font below): *"Tumor biopsy will be reviewed centrally to* ~~***confirm or***~~ *reconfirm diagnosis…"* The following bold language was added to Inclusion criteria 4: *"Participant agrees to provide archival or new tumor tissue for* ***re-confirmation*** *of disease."* The following bold language was updated in Section 8.1.3:	To clarify the requirement that the participant must have confirmed DT/AF prior to study entry.

	"Tumor samples will be used to ***~~confirm or~~*** *reconfirm desmoid diagnosis…"*	
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; and 8.2.2. Physical Examinations and Eastern Cooperative Oncology Group Performance Status.	The requirement for a brief physical exam has been removed and all physical exams will be complete.	Updated for clinical practice consistency. Per definition of the brief physical exam in the protocol, there was essentially no difference between the brief and complete exams.
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; and 8. Study Assessments and Procedures.	Urine pregnancy assessment added to the Cycle 1 Day 22 visit.	To correct a previous omission as monthly pregnancy testing is required monthly for women of childbearing potential (WOCBP).
1.3.1. Double-Blind Phase SoA; 6.3.1. Randomization; 6.5.1.3.2. Palliative Care 8. Study Assessments and Procedures; 8.1.1.1. Pre-Randomization RECIST v1.1 Calculation Worksheet.	Requirement for sites to complete a Pre-Randomization Tumor Assessment Calculation Worksheet during the screening period and required to be submitted to sponsor (or designee) at least 7 days prior to C1D1.	Implemented this worksheet to assist with additional documentation that a participant meets inclusion criteria 2 prior to randomization.
1.3.1. Double-Blind Phase SoA; and 8. Study Assessments and Procedures.	Requirement for the MRI assessment for tumor volumetric measurement changed from the baseline visit to the screening visit.	By moving the requirement for MRI to the screening visit, this allows an opportunity for the central imaging core laboratory assessment of the scans for quality prior to randomization.
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; and 8. Study Assessments and Procedures.	Requirement for study treatment accountability removed at Cycle 1 Day 8, Day 15, Day 22 and Cycle 2 Day 28.	Updated to align accountability with when participants are dispensed new study treatment, to align with site policies where tablets cannot be counted unless the bottle is being returned.
1.3.1. Double-Blind Phase SoA; and	The following screening visit language added:	To allow flexibility sites to extend the 28-day screening period (with

Study Assessments and Procedures.	*"An extension to the screening period will be permitted on a case-by-case basis following discussion between the investigator, medical monitor and/or the sponsor. The reason(s) for extension is to be clearly documented."*	medical monitor approval only) to conduct all screening assessments, including submitting the screening visit scans to the central imaging laboratory for a quality review prior to randomization.
1.3.1. Double-Blind Phase SoA; 8. Study Assessments and Procedures; and 8.1.2. Patient-Reported Outcomes.	Minimum screening period changed from 21 days to 14 days. Removed the requirement for a one-week break between the screening and baseline PROs.	To allow additional flexibility during the screening period, participants no longer have to wait an entire week between the screening and baseline PROs.
1.3.1. Double-Blind Phase SoA; and 1.3.2. Open-Label Extension Phase SoA; 5.2. Exclusion Criteria 3; and 8.2.3. Electrocardiograms.	Removed the following language: *"ECGs should be performed after vital signs and prior to blood draws, when applicable."* Added the following language (see bold font below): *"Triplicate 12-Lead ECGs readings (**approximately** 2-3 minutes apart and averaged)"*	To allow flexibility when EGCs need to be performed that aligns with standard of care procedures at the site.
2.2.3. Treatment; 2.4. Rationale for Participant Population and Placebo Arm; 4.2. Scientific Rationale for Study Design; and 9.2. Sample Size Determination.	Data from Phase 3 sorafenib study was updated (Gounder, 2018).	Publication available in The New England Journal of Medicine.
5.1. Inclusion Criteria.	Inclusion criteria 2 updated (refer to bold font below): *"Participant has **histologically confirmed** DT/AF **(by local pathologist prior to informed consent)** that has progressed by ≥ 20% as measured by RECIST v1.1 within ~~**the**~~ 12- **months of the screening visit scan** ~~period prior~~*	Added in the requirement for a participant to have histologically confirmed DT/AF prior to informed consent. Window for the requirement for the ≥ 20% progressive disease has been changed from 12

	~~to first dose of study treatment (nirogacestat or placebo).~~"	months prior to first dose of study treatment to 12 months prior to baseline scan. This will allow extra flexibility as the screening visit scan can be done anytime during the 28-day screening visit.
5.1. Inclusion Criteria; and Schema.	Inclusion criteria 3 updated (refer to bold font below): *"Participant has:* *a.* ***Treatment naïve ~~Newly diagnosed~~****, measurably progressing DT/AF that is* ***deemed*** *not amenable to* ***~~surgical resection or radiation therapy~~ surgery without the risk of significant morbidity;*** *OR* *b. Recurrent,* ***measurably*** *progressing DT/AF following* ***at least one line of therapy ~~CR to initial therapy~~;*** *OR* *c.* ***~~Preexisting~~ Refractory, measurably progressing*** *DT/AF* ***~~and has previously received therapy~~ following at least one line of therapy****.* ***~~and the residual tumor has progressed."~~***	a) "Newly diagnosed" changed to "Treatment Naïve" for additional clarity of the patient population. Removed radiation therapy to align with clinical care. b) "CR to initial therapy" changed to "following at least one line of therapy" because CRs are infrequent in desmoid tumors. c) "Preexisting DT/AF" changed to "Refractory, measurably progressing DT/AF" to reword for clarification. And "…the residual tumor has progressed" removed from the sentence due to redundancy.
5.1. Inclusion Criteria.	New inclusion criteria 4 added: ***"Participant has a DT/AF tumor where continued progressive disease will not result in immediate significant risk to the participant."***	Additional exclusion criteria added to ensure participant safety regarding progression.
5.1. Inclusion Criteria; 5.2. Exclusion Criteria; and 6.5.1.2. Excluded Concomitant Medications	Inclusion criteria 6, exclusion criteria 10 and Table 3 amended to require the wash-out period of investigational treatments or prior	To avoid overlapping toxicities with other therapies.

and/or Procedures (Table 3).	therapy to be within 28 days ***"(5 half-lives, whichever is longer) prior to first dose or)."***	
5.1. Inclusion Criteria.	Reference to the definition of occasional use of NSAIDs allowed in the study was removed from inclusion criteria and added to Table 3 instead. Inclusion criteria 7 was updated (refer to bold font below): **"~~or Occasional use (defined as ≤ 3 days per week) for the treatment of pain or as an anti-inflammatory in licensed conditions such as headache, arthritis, etc.~~"**	Moved out of inclusion criteria and into Table 3 as a footnote, as the inclusion criteria is referring to allowance of chronic NSAIDs as treatment for conditions other than DT/AF.
5.1. Inclusion Criteria; and 10.4. Appendix 4.	For inclusion criteria 11a, the requirement for males to use a double-barrier method of contraception has been replaced with the requirement to use a male condom. For inclusion criteria 11b, the requirement for women of child bearing potential (WOCBP) to use '2 forms of highly effective contraceptive methods' has been replaced with '1 highly effective contraceptive methods.' Footnote c in Appendix 4 was updated in the Contraception Guidance table to following update language (refer to bold font below): "***~~Two forms of highly effective birth control must be used throughout the study and during follow-up as specified for each gender (Inclusion Criteria 10).~~ Barrier methods such as condoms***	Given the potential for interaction between nirogacestat and hormonal contraceptives and a potential risk of reduced efficacy, a supplementary barrier method should be used by male partners in addition to the hormonal contraception method of participating WOCBP.

	(male or female) or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream or vaginal suppository must be used in addition to oral hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action."	
5.1. Inclusion Criteria.	The following additional language was added to inclusion criteria 11a: ***"An additional form of contraception as described in Section 10.4 should also be used by the female partner."*** The following language added to inclusion criteria 11b: ***The requirement for woman of child-bearing potential (WOCBP) to use 1 highly effective contraceptive method. In addition, a second method of contraception is required if the participant is using oral contraception, as coadministration with nirogacestat may result in reduced plasma concentrations of oral contraceptives and increase the risk of reduced efficacy.***	Following the Clinical Trial Facilitation Group (CTFG) guidance on contraception use during clinical trials, SpringWorks has assigned the highest risk category of demonstrated or suspected risk for human teratogenicity/fetotoxicity until results from reproductive toxicity studies become available. Per the guidance, women of child-bearing potential are required to use a highly effective method of contraception during treatment and until the end of relevant systemic exposure. An additional method of contraception is only required for female participants if their primary method of birth control is oral contraception, as coadministration of oral contraceptives and nirogacestat may result in reduced plasma concentrations of oral contraceptives and

		increase the risk of reduced efficacy. The protocol has therefore been revised to remove the requirement that all WOCBP use 2 methods of highly effective contraception and to specify that a second method is only required for women using oral contraception. This revision is consistent with the current guidance.
5.2. Exclusion Criteria.	Exclusion criteria 1 has been modified to clarify that participants should not undergo gastric procedures **that would alter absorption** of study treatment.	Added for additional clarity.
5.2. Exclusion Criteria.	A new exclusion criteria (exclusion 4) has been added to exclude the use of concomitant medications that prolong QT/QTc interval.	Amended to better align with ICH E14 document.
5.2. Exclusion Criteria.	A new exclusion criteria (exclusion 5) has been added to exclude participants with a history of additional risk factors for TdP.	Amended to better align with ICH E14 document.
5.2. Exclusion Criteria.	Exclusion criteria 7 (previously criteria 5) was updated to the following (refer to bold font): *"Lymphoma, leukemia, or any malignancy within the past 5 years* ***at the time of informed consent*** *except* ***for any locally recurring cancer that has been treated curatively (e.g., resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast), ~~basal cell or squamous~~***	Amended for additional clarity.

	~~epithelial carcinomas of the skin that have been resected~~ *with no evidence of metastatic disease for 3 years* ***at the time of informed consent****."*	
5.2. Exclusion Criteria.	Exclusion criteria 10 (previously criteria 6) updated to the following (refer to bold font): *"Participant is currently using* ***~~or anticipates using a~~ any treatment DT/AF including tyrosine kinase inhibitors (TKIs), NSAIs (chronic daily use) or any investigational treatment ~~after the observed progression (inclusion criteria 2) or within~~*** *28 days* ***(or 5 half-lives, whichever is longer).*** *prior to the first dose of study treatment* ***OR*** ***Participant has started a treatment for DT/AF after the documented DT/AF progressive disease (inclusion criteria 2)."***	Combined previous exclusion criteria 11 and 8 together as they are related.
5.2. Exclusion Criteria.	Exclusion criteria 10 (previously criteria 9) updated to: *"Participant is currently using or anticipates using food or drugs that are known strong/moderate cytochrome P450 3A4 (CYP3A4) inhibitors* ***or strong CYP3A inducers ~~(Section 10.7)~~*** *within 14 days prior to the first dose of study treatment."*	Combined previous exclusion criteria 9 with 10 as they are related.
5.2. Exclusion Criteria.	For exclusion criteria 12 the following language was updated (refer to bold font below) *"Participant is currently enrolled or was enrolled within 28 days of* ***first dose of study treatment***	Because not all observational studies may be allowed, this criterion was updated to require prior medical monitor approval.

	~~signing informed consent~~ *in another clinical study with any investigational drug or device.;* ***~~however, p~~*** *Participation in observational studies* ***may be~~ is~~*** *permitted* ***with prior approval from the medical monitor/sponsor."***	
5.2. Exclusion Criteria.	Inclusion criteria 17 was updated (refer to bold font): *"Participant with active* ***or chronic infection at the time of informed consent and during the screening period****.* ***~~bacterial, fungal, or viral infection including but not limited to the use of antibiotics, antifungals, or antiviral agents at the time of screening.~~****"*	Language amended to clarify the criteria.
5.2 Exclusion Criteria; and 6.1 (Table 2).	New exclusion criteria added (exclusion 19): ***"Participant has known hypersensitivity to the active substance or to any of the excipients of nirogacestat or placebo (Table 2)".*** The ingredients of Nirogacestat and Placebo added to Table 2.	Added for additional safety measures for participants.
5.2 Exclusion Criteria.	New exclusion criteria added (exclusion 20): ***"Participant is unable to comply with study related procedures (including, but not limited to, the completion of electronic patient report outcome (ePRO), or the ePRO questionnaires are not available in the participant's preferred language."***	Added to ensure participants who are able to complete all study assessments (including PROs) are being enrolled.
5.3.1. Meals and Dietary Restrictions.	The following section was added (Meals and Dietary Restrictions 5.3.1.):	The protocol excludes foods or drugs that are strong/moderate CYP3A4

	"Participants must refrain from consuming Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, or grapefruit hybrids at least 14 days prior to the first dose of study treatment and throughout the double-blind and open-label phase."	inhibitors and strong CYP3A4 inducers. Therefore, a Meals and Dietary Restriction section has been added to the protocol.
5.4. Screen Failures.	The following language added: *"Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at any time* ***if the participant has not screen failed on any of the following exclusion criteria: #1, 5, 6, 8, 9, 13, or 19."*** And The following additional language (refer to bold font below) was added with regards to their being no set limit to how many times a participant may be rescreened: ***"…and the screening assessments continue to be tolerable for the participant."***	Clarification around the requirement that the number of possible re-screenings must be limited to tolerable times.
6.1. Study Treatment(s) Administered.	Instructions updated: If a participant misses a scheduled dose of study treatment, and it is within **6 hours (increased from 2 hours)** they should immediately administer the missed dose.	Nirogacestat is rapidly absorbed and the majority of the administered dose is absorbed within the first few hours following dosing, the 2-hour window for administering the dose was too restrictive and may have led to a high level of missed doses. By expanding the window to 6 hours, it will not generate additional risk to the patient and will prevent unnecessary missed doses.

6.6. Dose Modification.	Table 4 updated: "~~***Other***~~ ***Any clinically significant*** *Grade ≥ 3 non-hematological toxicities"* Anaphylaxis added to the table with the intervention of permanently discontinuing study treatment. The following language removed from Grade ≥ 3 hematological toxicities "~~***Second episode: Permanently discontinue***~~."	Clarification added.
6.6. Dose Modification.	The following footnote was added to Table 4: ***"Refer to the study reference manual for guidelines on managing the AE of skin rash."***	Skin rash guidance provided for sites.
1.3.1. Double-Blind Phase SoA; and 1.3.2. Open-Label Extension Phase SoA; 8. Study Assessments and Procedures; and 8.5. Pharmacokinetics.	Additional PK sample added to the serial PK draws at hour 3.	The 3-hour PK sample was added to ensure the Cmax is captured in the majority of patients.
1.3.1. Double-Blind Phase SoA; and 1.3.2. Open-Label Extension Phase SoA; 6.1.1. Double-Blind Phase Dosing Administration; 6.1.2. Open-Label Phase Dosing Administration; and 8. Study Assessments and Procedures.	2-hour observation period updated to be a 3-hour observation period after the first dose.	To align with the additional PK draw at hour 3.
6.3.1. Randomization; and 8.1.1.2. Tumor Assessment Using RECIST Version 1.1 Criteria; and 10.8 Appendix 8: RECIST.	The following language was added: ***"The location of the target tumor(s) will be selected by the investigators as the basis for***	The majority (> 75%) of desmoid tumors are single foci; however, in the case of multi-focal there are instances when not all tumors are considered

	inclusion in the study and will be documented on the Pre-Randomization RECIST v1.1 Calculation Worksheet (Section 8.1.1.1).”	active. Treating physicians typically treat the active, progressing or symptomatic tumors. Therefore, the target tumor(s) that are actively being followed and assessed by the treating physician will be identified at screening and will be assessed throughout the study.
6.5.1.1.2.	New section added: ***“Nirogacestat has been shown to increase exposure of a sensitive CYP3A4 substrate, midazolam, by approximately 50% following multiple daily doses of 95 mg QD. The potential for nirogacestat to inhibit CYP3A4 in vivo following BID dosing at 150 mg has not been evaluated in a clinical study. However, using physiological-based pharmacokinetic modeling, nirogacestat was predicted to be a moderate inhibitor of CYP3A4 metabolism when administered at 150 mg BID resulting in increases in midazolam exposures ranging from 2- to 3.3-fold. Therefore, caution should be used when co-administering known CYP3A4 substrates with nirogacestat.*** ***Co-administration of CYP3A4 substrates with a narrow therapeutic index should be avoided if possible. If co-administration is unavoidable, the participant should be monitored closely for toxicity and investigator should consider***	Additional language has been added to the protocol to address the potential risk of nirogacestat to interact with drugs which are substrates of CYP3A4 at the clinical dose of 150 mg BID.

	reducing or titrating the dose of the substrate as necessary."	
6.5.1.1.4. Other Concomitant Therapy.	The following language has been added: ***"Nonclinical studies suggest that nirogacestat may induce CYP3A4, CYP2B6, CYP2C8 and CYP2C9 enzymes. Drugs which are substrates of these enzymes may have a reduced exposure/efficacy when co-administered with nirogacestat. Dose adjustments of these medications should be considered when appropriate.***	New information has been obtained regarding the potential for nirogacestat to induce these CYP enzymes.
6.5.1.1.4. Other Concomitant Therapy.	The following language has been added: ***"The effect of nirogacestat on the exposure of oral contraceptives has not been evaluated. However, induction of these CYP enzymes has been associated with reduced plasma exposure of various oral contraceptives resulting in reduced efficacy."***	New information has obtained suggesting that nirogacestat may induce CYP enzymes which are involved in the metabolism of various oral contraceptives.
6.5.1.1.4. Other Concomitant Therapy.	The following paragraph has been amended (refer to bold font below): *"Therefore, caution should be used when co-administering the study treatment with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol,* ***~~clarithromycin, conivaptan, diltiazem~~****, elacridar,* ***~~erythromycin~~****, felodipine,* ***~~itraconazole~~****, mibefradil,* ***~~nifedipine~~****, nitren**dipine, quinidine, ranolazine, talinolol,* ***and*** *valspodar,* ***~~and verapamil or strong P-gp inducers such as rifampin and St. John's Wort.~~***	P-gp list has been corrected. In vitro assays indicate that nirogacestat may inhibit P-gp at clinically relevant concentrations.

	Nonclinical studies have also indicated that nirogacestat may also be an inhibitor of P-gp and may increase the exposure of some P-gp substrates."	
6.5.1.1.4. Other Concomitant Therapy.	The following language has been added: ***"Co-administration of gastric acid reducing agents such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, etc.) may reduce the absorption of nirogacestat. These drugs should be avoided if possible or, when necessary, administered 2 to 4 hours following the morning dose of study treatment."***	Because nirogacestat is poorly soluble at higher pHs, administration of gastric acid reducing agents prior to dosing of nirogacestat may reduce absorption and lower exposure. Dosing of the agents in the morning is preferred so that the pH in the stomach and upper intestine is allowed to reduce prior to administration of the second daily dose of nirogacestat.
6.5.1.3.2. Palliative Care.	A new section was added: ***"During the double-blind and OLE phase of the study, systemic therapy or local therapy to the DT/AF tumors are not permitted.*** ***Medications for the standard management of symptoms or supportive care for the management of the effects of study treatment may be administered at the investigator's discretion; unless they are excluded concomitant medications (Section 6.5.1.2).*** ***Palliative radiation therapy may be permitted for pain or severe symptom control after consultation with the medical monitor/sponsor. Radiation will be limited to non-target lesions only and will be documented in***	Palliative care section added to provide sites with additional guidance on what is allowed in the study and what is not.

	the eCRF and on the Pre-Randomization RECIST v1.1 Calculation Worksheet. ***Surgical resection of non-target lesions will only be considered in exceptional circumstances after discussion with the medical monitor/sponsor and must not be as a consequence of disease progression.*** ***Thus, the following therapies are not permitted during the double-blind or OLE phases of the study:*** ***•Other anti-neoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy or other antibodies;*** ***•Potentially curative radiotherapy;*** ***•Surgical resection of DT/AF tumors; and*** ***•Any other investigational therapy."***	
6.6. Dose Modification	The following language was amended (refer to bold font below): ***If a participant experiences an AE as described in Table 4, hold study treatment until the AE is resolved to ~~Interruption of study treatment will continue until the toxicity is resolved~~*** *to ≤ Grade 1 or baseline.* ***If the AE is resolved within 14 days, then study treatment should be restarted at the reduced dose as described in Table 4. If the AE does not resolve to ≤ Grade 1 or baseline after holding study treatment for 22 days, study treatment may be resumed only ~~A delay of study treatment for more than 14 days~~***	This section was reworded for clarity to provide sites with better guidance on dose modification requirements.

	~~***due to any toxicity may require permanent discontinuation. After 14 days of interruption, study treatment may be resumed***~~ *only after discussion with the medical monitor/* ~~***and approval by the sponsor.***~~ ~~***After interruption, doses of study treatment may be resumed at a reduced dose of 100 mg BID.***~~ *Should the same* ~~≤~~ *≥ Grade 3* ***AE*** ~~***toxicity***~~ *recur at* ~~***the reduced dose 100 mg BID,***~~ *and the* ***AE*** ~~***toxicity***~~ *is considered related to the study treatment, study treatment may be* ***permanently*** *discontinued following discussion with the medical monitor/* ~~***and sponsor. If the same toxicity does not recur within 14 days, study treatment can resume to 150 mg BID.***~~
6.6. Dose Modification.	The following sentence was amended (refer to bold font below): *"Every effort will be made to administer study treatment* ***(nirogacestat or placebo)*** *at 150 mg BID. However* ~~***, in the event of significant toxicity***~~*, dosing* ***will*** ~~***may***~~ *be interrupted and/or dose reduced* ***for the AEs*** ~~***as***~~ *described in Table 4."*	Clarified that dose modifications are required in the event of an AE as described in Table 4.
6.6. Dose Modification.	Second paragraph: The following sentence was corrected from *"Should the same* ***≤ Grade 3*** *toxicity recur at 100 mg BID…"* To: ***"****Should the same* ***≥ Grade 3 AE*** *at 100 mg BID…"*	Corrected previous error.

7.1. Discontinuation of Study Treatment.	***"Any grade ≥ 3 hypersensitivity reaction"*** was added to the fifth bullet (reasons why a participant is unblinded for safety reasons).	Inadvertently omitted.
8. Study Assessments and Procedures.	Amount of blood collected from each participant has been increased from approximately 169 mL to 193 mL each year for the double-blind phase and increased from 136 mL to 160 mL each year for the OLE phase.	Updated with additional PK blood draw required (3-hour post dose).
8.3.6. Adverse Events of Special Interest.	New section to describe what the adverse events of special interest are for the study and how to report them.	Adverse Events of Special Interest (serious or non-serious) have been added because they are of scientific and medical interest for nirogacestat, for which ongoing monitoring and further investigation will help to characterize and better understand the safety profile.
8.4. Treatment of Overdose.	Following sentence changed (refer to bold font below): ***"****For this study, any dose of study treatment greater than* ~~***300***~~ ***450*** *mg daily dose of study treatment within a 24-hour period will be considered an overdose."*	Changed to 450 mg since the maximum tolerated dose in the phase 1 study was 220 mg BID.
8.5. Pharmacokinetics.	The following additional language was added (refer to bold font below) ***"****Samples will be used to evaluate the PK of nirogacestat* ***and associated metabolites."***	New information.
ADMINISTRATIVE CHANGES AND CLARIFICATIONS		
Section # and Name	**Description of Change**	**Brief Rationale**
Protocol Amendment Summary of Changes Table.	Deleted Protocol Amendment 1 (27Nov2018) summary of changes.	Amendment 1 summary of changes are no longer applicable. Amendment 2

		summary of changes has been added addendum.
Sponsor Signatory; and 10.10.3. Medical Monitoring.	Medical Monitor signatory change from Frank Smith, MD to Greg Hale, MD, and contact information updated.	Medpace Medical Monitor personnel change.
1.1. Synopsis; 1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; 3. Objective and Endpoints; 8.1.2.1. GODDESS; and 9.4.1. Efficacy Analyses.	MSK/DTRF DTSS and DTIS has been changed to GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS).	Updated to reflect new name of the PRO.
1.1. Synopsis; and 4.1.1. Overall Design for the Double-Blind Phase.	The following paragraph was added to the Overall Design of the Synopsis: ***"If Central Imaging Review determines that a participant has progressive disease (using RECIST v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will return to the site for an end of treatment (EOT) visit within 14 days of the notification. During the EOT visit, the participant will be unblinded and have the option to enter the OLE phase if eligible (Section 6.7.1)."***	Added additional clarity on the operational aspects of the study.
Throughout the protocol	All references to ***"confirmed by central review"*** has been updated to ***"determined by Central Imaging Review."*** References to ***"disease progression"*** has been updated to ***"progressive disease"*** when referring to a participant meeting progressive disease.	Updated terminology for consistency with imaging manuals and RECIST v1.1.

	References to the central imaging has been changed to ***"central imaging core laboratory"***	
1.1. Synopsis.	The following footnote to the Schema was added: *"All eligible participants must have histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan (inclusion criteria 2."*	Added for additional clarity.
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; and 8. Study Assessments and Procedures.	Description for laboratory assessment of ***"****blood for* ***clinical chemistry"*** changed to ***"****blood for* ***safety labs."***	Updated for additional clarification as these labs include hematology and serum chemistry and therefore, "safety labs" better described the assessment.
1.3.1. Double-Blind Phase SoA; and 8. Study Assessments and Procedures.	The following language was added: *"The date the participant signs the ICF will be Day 1 of the screening period."*	Added for additional clarity.
1.3.1. Double-Blind Phase SoA; and 1.3.2. Open-Label Extension Phase SoA.	The following language was added to the footnote of the SoA tables (see bold font below): *"Height: Required at screening only.* ***Weight to be collected at all visits.****"*	Added for additional clarity.
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA 8. Study Assessments and Procedures; and 8.2.6. Pregnancy Testing.	The following language has been updated regarding the monthly urine pregnancy tests (see bold font below): *"If more convenient for the participant, they may alternatively visit a* ~~***sponsor approved***~~ *local laboratory* ***that has been pre-approved by the sponsor (or***	Sentence has been updated to provide additional clarity on the monthly urine pregnancy tests that are required throughout the study if the participant would prefer to visit a local laboratory for the assessment.

	designee) *for this assessment* ***(refer to the study reference manual for additional details).”***	
1.3.1. Double-Blind Phase SoA; 1.3.2. Open-Label Extension Phase SoA; and 6. Study Treatment.	The following language added (see bold font below): *Participants will complete the questionnaires* ***and record study treatment administration in the eDiary*** *using the home ePRO device.*	Added for additional clarity around how the participant will record their daily dosing of study treatment throughout the study.
1.3.1. Double-Blind Phase SoA.	The following language has been added to the SoA footnote for imaging *“MRI and CT scans obtained during the screening visit will serve as the participant’s baseline scan for the study (CT scan only required if it’s the chosen modality for RECIST v1.1 tumor measurement). Scans should be submitted to central imaging core laboratory as early in the screening period as possible to confirm scan quality is acceptable for analysis prior to randomization.”*	Added for additional clarity around operational logistics regarding the screening scan requirements.
1.3.1. Double-Blind Phase SoA; 8. Study Assessments and Procedures; and 8.1.1. Tumor Imaging.	The following language was updated (refer to bold font below): ***“Standard of care*** *scan(s) acquired prior to the participant signing ICF may be used as the participant’s screening visit* ***~~timepoint~~*** *scan(s) if obtained within 28 days of the first dose study treatment* ***and the quality of the scans are acceptable for analysis (as determined by the central imaging core laboratory).”***	Added clarity that if a scan is going to be used for the screening scan on study, then it must be a standard of care scan with acceptable quality as determined by central imaging review.
1.3.1. Double-Blind Phase SoA.	The following language was added to the SoA footnote for imaging:	Added for additional clarity.

	"Starting at cycle 4, MRI or CT scans for tumor assessment (RECIST v1.1) will be obtained every 3 cycles. Starting at cycle 7, MRI for tumor volume assessment will be obtained every 6 cycles."	
1.3.2. Open-Label Extension Phase SoA; and 4.1.2. Overall Design for the Optional OLE Phase	The following sentence was amended: ***"The C1D1 visit of the OLE phase should be conducted on the same day as ~~T~~the double-blind EOT visit. ~~will serve as the OLE baseline visit.~~"***	Added for additional clarity.
4.1.1. Overall Design for the Double-Blind Phase.	The following language was added (refer to bold font below): *"Following the baseline visit (Cycle 1 Day 1), participants will return to the clinic for study visits at Cycle 1 (Days 8, 15, 22), Cycle 2 (Day 28),* ***Cycle 4 (Day 1)*** *and* ***then*** *on Day 1 of every 3 cycles thereafter."*	Previous omission.
4.1.1. Overall Design for the Double-Blind Phase.	The following footnote was added: *"When the required number of PFS events have been observed and the primary PFS analysis has been completed, all remaining participants in the double-blind phase will be unblinded. And if eligible, they will have the option to enter the OLE phase."*	Added to better describe the logistical aspect of the study for when the required number of PFS events are met.
4.1.2. Overall Design for the Optional OLE Phase.	The following paragraph was added as well as additional operational details regarding the OLE Phase: *"Participants will be enrolled in the OLE phase using the IRT only after (1) all ongoing AEs/SAEs from the double-blind phase have been assessed for causality in a blinded manner by the investigator*	Additional details added to better describe overall design of the OLE phase.

	or qualified designee, and (2) all AE/SAE causality assessments have been entered into the electronic case report form (eCRF). In addition, all double-blind EOT visit assessments must be completed prior to unblinding and administering the first dose of open-label study treatment. Refer to Section 6.3.2.1 for more detail on the required unblinding criteria."	
5.1. Inclusion Criteria; 5.2. Exclusion Criteria; and 6.5.1.2. Excluded/Restricted Concomitant Medications and/or Procedures (Table 3).	Reference to "observed progression" was changed to " documented DT/AF progressive disease (inclusion criteria 2)."	Amended for clarity purposes.
5.1. Inclusion Criteria; and 10.2. Appendix 2: Clinical Laboratory Tests.	Inclusion criteria 8f has been updated to correct the creatinine clearance units (refer to bold font below). *"calculated creatinine clearance must be ≥60 mL/min~~**1.73m2**~~"*	Previous error.
6.1. Study Treatment Administered.	The following sentence was removed: ~~***"Missed doses will also be recorded in the home ePRO device."***~~	This sentence is misleading. If there is a missed dose, the device will capture it, but the participant or site will not be entering in a missed dosed.
6.1.1. Double-Blind Phase Dosing Administration.	Removed the following sentence: ~~***"Once the informed consent process (Section 10.1.3) for the double-blind phase has been conducted, all entry criteria have been met, and the randomized treatment assignment confirmed using IRT…"***~~	Sentence not necessary in this section. The process of what steps need to be completed prior to randomization has been added to section 6.3.1.
6.1.2. Open-Label Phase Dosing Administration.	First paragraph removed describing the OLE overall study design.	This paragraph did not belong in this section and

		is already described in Section 4.1.2.
6.1.3. Study Treatment Errors.	The following language was added: ***"Missed doses are not considered dosing errors."*** The following language was removed: ***"Whether or not the study treatment error is accompanied by an AE (as determined by the investigator), the study treatment error (if applicable), and any AE(s), must be captured on an AE eCRF page."*** And the following sentence added: "***All study treatment errors will be captured on an AE eCRF page."***	For additional clarity to simplify.
6.2. Preparation / Handling / Storage / Accountability; 6.3.1. Randomization.	The following sentences were moved from section 6.3.1 to 6.2: ***"Study treatment will be dispensed to participants every 3 cycles during scheduled study visits as described in the SoA (Section 1.3) or unscheduled visits if study treatment is damaged/lost or dose modification (Section 6.6) is necessary."*** ***"Returned study treatment will not be re-dispensed to the participants."***	Language did not fit in section 6.3.1.
6.3.1. Randomization.	The following language was added to this section: ***"Prior to participants being randomized to study treatment,***	Added additional clarity on the operational aspects of the study with regards to randomization.

	the following activities must be completed: ***1. Participant must sign the ICF (Section 10.1.3) and complete all screening assessments (Section 1.3.1).*** ***2. Site must submit the Pre-Randomization RECIST v1.1 Calculation Worksheet at least 7 days prior to Cycle 1 Day 1 (Section 8.1.1.1).*** ***3. Site must submit the screening visit scan(s) to the central imaging core laboratory as early in the screening period as possible to confirm scan quality (Section 8.1.1).*** ***4. Site must confirm that the participant meets all study entry criteria (Sections 5.1* and 5.2).** **5.** ***Participant must complete all pre-randomization baseline visit assessments. Refer to Section 1.3.1 and Baseline and Cycle 1 Day 1 (double-blind phase) for additional details."*** ***"If the participant has multiple primary tumors that are located both in the intra- and extra-abdominal location, the tumor should be classified as intra-abdominal."***	
6.3.2. Blinding.	The following language was added: ***"If Central Imaging Review determines that a participant has progressive disease (using RECIST v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will then return for the EOT visit which will be***	Added for additional clarity of what is required if a participant has progressive disease (as determined by Central Imaging Review), and they will not be unblinded if they do not have progressive disease (as determined by Central Imaging Review).

	conducted in a completely blinded fashion. All EOT assessments and all ongoing AEs/SAEs must (1) be assessed for causality by the investigator or qualified designee in a blinded manner and (2) recorded in the eCRF prior to the unblinding of the study treatment allocation (Section 6.3.2.1). ***If a participant discontinues study treatment for any reason other than progressive disease (as determined by Central Imaging Review using RECIST v1.1.), the study treatment allocation will not be unblinded."***	
6.3.2.1. Breaking the Blind.	Added in the following language (refer to bold font below): *"The study treatment blind is not to be broken* ***~~during the double-blind phase~~*** *unless one of the following criteria apply (unblinding at the clinical site for any other reason****~~s during the double-blind phase~~*** *will be considered a protocol deviation* ***and the unblinded participant will be permanently discontinued from the study****)"*	Amended this sentence to make it clear that if a participant is unblinded for any reason other than progressive disease (as determined by Central Imaging Review) they will be permanently discontinued from the study.
6.4. Study Treatment Compliance.	This section has been reworded and additional language added: ***"If the participant is not compliant with study treatment dosing, the site must re-educate the participant on proper dosing compliance and its importance. Continued non-compliance may lead to withdrawal of the participant from the study, after consultation between the***	Added details around compliance and non-compliance to provide sites with additional guidance if a participant is not compliant with study treatment.

	investigator and the medical monitor/sponsor."	
6.4. Study Treatment Compliance.	The following sentence was amended (refer to bold font below): *"The number of tablets dispensed, and the number of tablets returned will be recorded in the eCRF**~~, as well as any deviations~~**."*	Deviations for missed doses are not captured in the CRF. Compliance (or non-compliance) by way of tablet count will be captured in the CRF instead.
6.5.1.2. Excluded/Restricted Concomitant Medications and/or Procedures.	Table 3 has been re-organized and additional restricted/excluded medications/procedures have been pulled into this table from Section 6.5.	Amended table for simplicity and completeness of all the restricted/excluded medications/procedures that are listed in Section 6.5.
7.2. Participant Discontinuation/Withdrawal from the Study.	The following sentence was added (refer to bold font below): *"If a participant withdraws from the study, they may request destruction of any samples taken and not tested. **The sponsor must be notified if the participant requests destruction of sample**, and the investigator must document this in the site study records."*	Added f or additional instructions for the sites to take if a participant withdraws from the study.
8. Study Assessments and Procedures.	Table 6 and 7 were re-organized and updated to additional operational logistics pulled in from the SoA table.	Tables were updated to provide additional operational reminders to assist the sites when conducting study visits. These updates were mainly pulled in from the SoA table or already existing instructions from study manuals etc.
8. Study Assessments and Procedures (Table 6).	Removed the following statement from Table 8 (the screening visit): ***~~"As a reminder, the screening scan (CT or MRI) must show ≥ 20% disease progression~~***	Incorrect statement that does not reflect inclusion criteria #2 properly, as the ≥ 20% disease progression entry criteria does not have to be measured using

	~~(measured by RECIST v1.1) compared to a historical scan obtained within the 12 months prior to first dose of study treatment (refer to double-blind inclusion criteria 2).”~~	the screening scan. Participants must have shown ≥ 20% disease progression over the past 12 months of screening visit scan (using any two scans).
8.1.1. Tumor Imaging.	Additional details regarding Imaging requirements have been added to this section.	Logistical details as well as information from the study manuals have been added to this section for additional clarity and expectations for sites.
8.1.2. Patient-Reported Outcomes.	Removed the following sentence: ***“~~Refer to the study reference manual for more information on the PROs and the user guides for administration~~.”***	Previous error. There are no user guides that are provided in the study reference manual.
8.1.2. Patient-Reported Outcomes.	In Table 9, for quarterly PRO assessment columns, cycle 21 was changed to cycle 22.	Corrected typo.
8.1.3. Tumor Biopsy.	This section has been re-organized and the requirement for 15 slides to be made available has been changed to approximately 20.	Section has been re-organized and re-worded to provide better clarity around the biopsy requirement.
8.2.6. Pregnancy Testing; and 10.2. Appendix 2: Clinical Laboratory Tests.	The following language was added: ***“Serum pregnancy tests may be conducted in place of urine pregnancy tests throughout the study if required by local regulations.”***	Added to allow flexibility for those institutions that require serum pregnancy testing in lieu of urine pregnancy testing.
9.5.1. Data Monitoring Committee.	Administrative language added to align with DMC Charter.	To better align with DMC Charter.
10.3.3. Recording and Follow-Up of AE and/or SAE; and 10.3.4. Reporting of SAEs.	The following sentenced was reworded, ***“The investigator will then record all relevant AE/SAE information in the electronic case report form (eCRF),”*** to the following sentence, ***“All required information pertaining to the AE/SAE will be recorded in the***	For additional clarity.

	electronic case report form (eCRF). Additional language regarding how SAEs are to be reported to UBC has been added: ***"immediately, without undue delay, under no circumstances later than 24 hours after becoming aware of the event."***	
7.1. Discontinuation of Study Treatment; 7.1.2. QTc Stopping Criteria; and 8.2.3. Electrocardiograms.	Corrected references from QTc to QTcF.	Inadvertently omitted.
8.3. Adverse Events and Serious Adverse Events; and 10.3. 5. Definition of AR, SAR and SUSAR; and 10.10. Abbreviations.	Definitions for AR, SAR and SUSAR added.	Added for additional clarity.
8.5. Pharmacokinetics (Table 10).	PK requirement for Cycle 2 Day 1 corrected to Cycle 2 Day 28.	Corrected typo.
9.1. Statistical Hypotheses.	The following sentence was removed: ***"~~The null hypothesis will be rejected if the HR is > 0.4.~~"***	Removal of this sentence is because the hazard ratio is not the decision rule for rejecting the null hypothesis.
10.11. Protocol Amendment History.	The rationale for the following change in section 1.3.2 in protocol amendment 1 was inadvertently left out of the protocol amendment 1 rationale table: Requirement for the participant to return to the clinic for the EOT visit within 28 days of notification or as soon as possible for those participants who experience disease progression was removed.	To simplify the visit window for the EOT visit with regards to the OLE phase.
1.1. Synopsis; and 6.7.1. Optional Open-Label Extension Phase.	Reference and link to Table 7 was added to overall design of the OLE study.	Inadvertently omitted.

10.11. Protocol Amendment History.	Protocol amendment history removed.	Amendment 1 summary of changes are no longer applicable. Amendment 2 summary of changes has been added as a separate document.
10.1.8. Appendix 1: Study and Site Closure.	Study termination criteria added.	To provide additional clarity around when the sponsor may terminate the study overall.
5.2. Exclusion Criteria; 6.5.1.1.1. Cytochrome P450 Inhibitors and Inducers; 6.5.1.1.3. Anti-Emetic and Anti-Diarrheal Therapy; 6.5.1.2. Excluded Concomitant Medications and/or Procedures; and Appendix 7.	Removed references to Section 10.7	Link to medicine.iupui.edu was removed, as this website is not inclusive of all CYP3A4 inhibitors and inducers that are excluded in the protocol. Sites will need to reference the package inserts for concomitant medication to confirm if allowed per protocol.
10.10. Appendix 10: Abbreviations.	Abbreviation table updated.	New abbreviations.
10.1.3. Informed Consent Process.	Following sentence removed: ~~***"A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date."***~~	Previous error. If participant screen fails, they must obtain a new screening number and sign a new consent at time of rescreen.

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Protocol: NIR-DT-301

Amendment 3 Summary and Rationale

Date of Amendment: 27 January 2020

This amendment is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Apart from minor edits, formatting changes and necessary editorial updates, the following changes were made to the protocol amendment 2 (14Oct2019):

Rationale for the Amendment:

SUBSTANTIAL CHANGES		
Section # and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities	Added the following text (in bold font below): *Medical history* ***including menstrual history for women***	Added for clarification to ensure menstrual irregularities are captured as part of the medical history, as applicable.
1.3 Schedule of Activities	Added blood sampling for hormone level laboratories for males and females in the double-blind and open-label phases of the study. Added the following text (in bold) with regards to hormone level testing: ***The time of hormone level blood draws should also be recorded.***	Clinical laboratories to monitor hormone levels were added to the protocol in response to reported events of primary ovarian insufficiency.
1.3.2 Schedule of Activities for Open-Label Extension Phase	Added the following text (in bold) for the open-label phase Baseline visit: *Baseline visit: The C1D1 visit of the OLE phase should be conducted on the same day as****, or within 24 hours after,*** *the double-blind EOT visit.* ***A longer window between the double-blind EOT and OLE C1D1 visit may be***	Updated language to allow for flexibility in scheduling the double-blind EOT and open label C1D1 visits based on investigator feedback.

	allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1.	
2.5 Benefit/Risk Assessment	The following language was added to the benefit/risk assessment (see bold font below): *Based on the mechanism of action and nonclinical/clinical study data, the important identified risks associated with nirogacestat administration include* ***notch-related effects on reproductive function and fertility,*** *notch-related effects on hematopoietic (immune) function, notch-related effects on gastrointestinal function, skin rash, and hypophosphatemia.* ***The study will utilize an independent data monitoring committee (DMC) and will operate according to an established Charter (Section 9.5.1). In addition, a protocol steering committee was established to support the development of nirogacestat for the treatment of desmoid tumor/aggressive fibromatosis. The purpose and provisions of the DMC will be specified in the DMC Charter.***	Based on nonclinical data and events of primary ovarian insufficiency reported in women receiving nirogacestat, notch-related effects on reproductive function and fertility were added as risks associated with nirogacestat. Language was also added to clarify the oversight of the DMC and Steering Committees in monitoring the ongoing clinical study and overall nirogacestat development.
4.1.2 Overall Design for the Optional OLE Phase	Added the following language (bold font): *The Cycle 1 Day 1 visit of the OLE phase should be conducted on the same day as,* ***or within 24 hours***	Updated language to allow for flexibility in scheduling the double-blind EOT and open label C1D1 visits.

	after, *the double-blind EOT visit.* ***A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1.***	
5.1 Inclusion Criteria	Added the following text (in bold) to inclusion criterion 11: Males: • *Refrain from donating* ***or preserving*** *sperm;* Females: • *Is of childbearing potential but is abstinent or using 1 highly effective contraceptive method, as described in Section 10.4 during the treatment period and until ~~30 days~~* ***6 months*** *after the last dose of* ***active*** *study treatment. A second method of contraception is required if the participant is using ~~oral~~* ***hormonal*** *contraception, as coadministration with nirogacestat may alter the plasma concentrations of ~~oral~~* ***hormonal*** *contraceptives resulting in reduced efficacy. Additionally, the participant agrees not* ***to harvest or*** *donate eggs (ova, oocytes) for the purpose of reproduction during the treatment period and for at least ~~60 days~~* ***6 months*** *after the last dose of* ***active*** *study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.*	Clarified language to ensure the same guidelines were followed for egg / sperm donation or preservation for reproductive intent. Increased the recommended timeframe between receipt of active study drug and pregnancy and/or egg harvest/donation for females from 60 days after the last dose of active study treatment to 6 months after the last dose of study treatment to ensure sufficient time for nirogacestat clearance and resolution of potential hormone changes which may be associated with study treatment prior to fertility preservation. Clarified that a barrier method of contraception should be used in addition to hormonal contraception (not just oral contraception) per Clinical Trial Facilitation Group (CTFG) guidelines.

5.2 Exclusion Criteria	Revised exclusion criterion 4 by adding the following text (in bold): *Participant is using concomitant medications* ***that are known*** *to prolong the QT/QTcF interval* ***including Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) antiarrhythmics*** *at the time of informed consent.* ***Non-antiarrhythmic medications which may prolong the QT/QTcF interval are allowed provided the participant does not have additional risk factors for Torsades de Pointes (TdP).***	Added language to define the excluded concomitant medications which are known to prolong the QT/QTcF interval.
6.5.1.2 Excluded/Restricted Concomitant Medications and/or Procedures Table 3	Updated the following language (bold text): ~~*Concomitant*~~ ***Antiarrhythmic*** *medications that* ***are known to*** *prolong the QT/QTcF interval* ***including: Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) antiarrhythmics;***	Updated language regarding concomitant medications which known to prolong the QT/QTc interval for consistency with inclusion criterion 4.
6.5.1.3.2 Palliative Care	Updated the following language (bold text): *Palliative radiation therapy may be permitted* ~~*for pain or severe symptom control*~~ ***in the OLE phase of the study*** *after consultation with the medical monitor/sponsor. Radiation will be limited to non-target lesions only and will be documented in the eCRF and on the Pre-Randomization RECIST v1.1 Calculation Worksheet.* ~~*Surgical resection of non-target lesions will only be considered in*~~	Updated language to clarify that palliative radiation will only be allowed in the open-label phase of the study. Surgical resection will not be allowed in either phase of the study as this could potentially impact the overall tumor assessments.

	~~*exceptional circumstances after discussion with the medical monitor/sponsor and must not be as a consequence of disease progression.*~~	
6.6 Dose Modifications	Added the following language (bold text): ***Study treatment may also be modified to manage other AEs in collaboration with the medical monitor.*** Added reproductive system toxicities including Grade ≥ 2 premature menopause / primary ovarian insufficiency to the table of allowed dose modifications. The following text (in bold) was added as a footnote to the dose modification table: ***A dose reduction is not required for events of premature menopause / primary ovarian insufficiency but may be considered for symptomatic participants based on the individual benefit / risk profile. A dose interruption is not required prior to a dose reduction for reproductive system toxicities.***	Added language to allow for dose modifications for the treatment of AEs with advance medical monitor approval. Added reproductive system toxicities including Grade ≥ 2 premature menopause / primary ovarian insufficiency to the table of allowed dose modifications for symptomatic participants based on the individual benefit/risk profile.
Section 8 Study Assessments and Procedures.	Amount of blood collected from each participant has been increased from approximately 193 mL to 218 mL each year for the double-blind phase and increased from 160 mL to 180 mL each year for the OLE phase.	Updated with the hormone level laboratories requirement (as noted in the Schedule of Activities).
Section 8 Study Assessments and Procedures Table 6	Added hormone level assessments to the list of blood draws for safety laboratory parameters.	Clinical laboratories to monitor hormone levels were added to the protocol in response to recent

		events of primary ovarian insufficiency.
Section 8 Tables 6 and 7	Added the following language (in bold): *Eligible participants may enter the OLE phase at this time. The EOT visit should be conducted on the same day as**, or 24 hours prior to,** as the C1D1 visit for the OLE phase. **A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1.**	Updated language to allow for flexibility in scheduling the double-blind EOT and open label C1D1 visits.
8.2.1 Demographic Data and Medical History	Added the following language (in bold): ***For women, the medical history should also include a detailed menstrual history including the date of the last menstrual cycle and any history of amenorrhea, menstrual irregularities, or infertility. Any history of infertility in male participants should also be recorded as part of the medical history.***	Added for clarification to ensure any history of menstrual irregularities or infertility are captured as part of the medical history, as applicable.
8.2.5 Clinical Safety Laboratory Assessments	Added the following text for clarity: *"All protocol-required, central laboratory assessments as defined in Section 10.2 must be conducted in accordance with the central laboratory manual and the SoA.* ***Please note, ALL participants, regardless of their gender or childbearing potential, are required to have hormone level***	Clinical laboratories to evaluate hormone levels were added to monitor for events of primary ovarian insufficiency.

	assessments per the SOA (Section 1.3)."	
8.3.6 Adverse Events of Special Interest	Added reproductive system disorders including amenorrhea and premature menopause / primary ovarian insufficiency as adverse events of special interest. Added the following text for clarity: ***"AESIs will be followed until resolution or return to baseline."*** Removed gastrointestinal events including nausea, vomiting/dyspepsia, and diarrhea, as AESIs.	Reproductive system disorders including amenorrhea and premature menopause / primary ovarian insufficiency were added as adverse events of special interest to enable additional safety follow-up. Gastrointestinal events were removed as AESIs as these are now known and expected events related to nirogacestat. These events are expected to occur and will be tracked for severity. These events will also be reported as serious adverse events if they meet SAE reporting criteria.
10.2 Appendix 2: Clinical Laboratory Tests	Added the following clinical laboratory assessments for women: • TSH • Prolactin • AMH • LH • FSH • Estradiol • Progesterone Added the following clinical laboratory assessments for men: • Total testosterone • Free testosterone • Progesterone • FSH • LH	Clinical laboratories to monitor hormone levels were added to the protocol in response to events of primary ovarian insufficiency.

	The following footnotes were also added to the table of assessments (in bold): ***6) Hormone level assessments for both females and males are required per the SoA in Section 1.3.*** ***7) Female hormone levels for TSH and prolactin are only required at Screening and EOT.***	
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added the following language in bold: *Any abnormal laboratory test results (hematology, clinical chemistry, **hormone levels**, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).*	Added hormone levels to the list of laboratories abnormalities that would result in AE reporting.

10.3.5 Definition of AR, SAR, and SUSAR	Revised the definitions of serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR): *Serious Adverse Reaction (SAR):* ***A SAR is an SAE for which a causal relationship with the product or procedure is at least a reasonable possibility (i.e., the relationship cannot be ruled out)****.* ~~*An SAR is any noxious and unintended response to a medicinal product which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death.*~~ *Suspected Unexpected Serious Adverse Reaction (SUSAR):* *A SUSAR is a* ~~*any*~~ *SAR* ~~*for which there is a reasonable possibility that the drug caused the SAR. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the SAR*~~ ***is judged as unexpected. An event is*** ~~*SUSAR*~~ *is considered "unexpected" if it is not listed* ***as expected in the reference safety information (RSI) section of*** ~~*in*~~ *the investigator brochure (IB)* ~~*or is not listed at the specificity or*~~	Updated to correct error.

	~~*severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" in this context also refers to reactions that are referred to in the IB as occurring with a class of drugs or as anticipated from the pharmacologic properties of the drug, but not as occurring specifically with the drug under investigation*~~ ***summary of product characteristics.***	
ADMINISTRATIVE CHANGES AND CLARIFICATIONS		
Section # and Name	**Description of Change**	**Brief Rationale**
Sponsor Signatory	Replaced L. Mary Smith with Allison Lim as the Sponsor signatory.	Updated to reflect new SpringWorks personnel.
10.9 Abbreviations	Added new abbreviations for AMH, LH, and TSH.	Updated to reflect new abbreviations.
5.2 Exclusion Criteria	Added the following language to exclusion criterion 10 (in bold): *Participant is currently using any treatment for DT/AF including tyrosine kinase inhibitors (TKIs), NSAIDs (chronic daily use –* ***except as in inclusion criterion 7****) or any investigational treatment 28 days (or 5 half-lives, whichever*	Updated for clarity

	is longer) prior to the first dose of study treatment.	
6.1 Study Treatment Administered	Added the following text (in bold): *If more than 6 hours have elapsed since the time of scheduled administration, the participant should be instructed **not** to administer the missed dose and to resume study treatment as prescribed.*	Updated to correct inadvertent omission
6.3.1	Added the following text (in bold): *Extra-abdominal (including head/neck, para-spinal, extremities, abdominal **wall,** chest wall, and other locations).*	Updated for clarity.
6.5.1.1.4 Other Concomitant Therapy	The following language was revised: *The effect of nirogacestat on the exposure of ~~oral~~ **hormonal** contraceptives has not been evaluated. However, induction of these CYP enzymes has been associated with reduced plasma exposure of various ~~oral~~ **hormonal** contraceptives resulting in reduced efficacy.* *Nonclinical studies have indicated that nirogacestat is a substrate for the drug efflux transporter P-glycoprotein (P-gp). Therefore, caution should be used when co-administering the study treatment with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, elacridar, felodipine, mibefradil, nitrendipine, quinidine, ranolazine, talinolol, **and** valspodar, d~~igoxin, dabigatran, and fexofenadine~~. Nonclinical studies have indicated that*	Updated for clarity.

	*nirogacestat may **also** be an inhibitor of P-gp and may increase the exposure of some P-gp substrates **like digoxin, dabigatran, and fexofenadine; participants receiving these medications should be closely monitored.***	
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Added the following text (in bold): *Women in the following categories are not considered WOCBP:* 1. *Premenarchal* 2. *Premenopausal female with 1 of the following:* • *Documented hysterectomy; or* • *Documented bilateral salpingectomy; or* • *Documented bilateral oophorectomy.* *For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.* ***Bilateral tubal occlusion is not considered to be a permanent form of infertility.*** *Note: Documentation can come from the site personnel's review of the participant's medical records, medical*	Updated for clarity.

	examination, or medical history interview.	
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Moved the following footnote from being specific to oral contraceptives to pertaining to all combined hormonal contraception: *Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]* • *Oral[e]* *c) Barrier methods such as condoms (male or female) or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream or vaginal suppository must be used in addition to ~~oral~~ hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.*	Corrected typographical error

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Protocol: NIR-DT-301

Amendment 4 Summary and Rationale

Date of Amendment: 07 July 2020

This amendment is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Apart from minor edits, formatting changes and necessary editorial updates, the following changes were made to the protocol amendment 3 (27Jan2020):

Rationale for the Amendment:

SUBSTANTIAL CHANGES		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis Objectives and Endpoints AND 3 Objectives and Endpoints (Table 1)	Made the following revisions to the definition of disease progression in the primary endpoint (added text in bold font below): *PFS defined as the time from randomization until the date of assessment of progression or death by any cause will be determined.* ***Progression will be determined radiographically*** *using Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1 (Eisenhauer, 2009; Section 10.8)* ***or clinically as assessed by the investigator. Clinical progression occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status.***	Given the unique characteristics of DT/AF including its ability to grow in an asymmetric manner, applying RECIST v1.1 alone is not adequate in capturing the entirety of disease progression and its clinical impact on patients. To account for this limitation, the definition of disease progression in the primary endpoint was updated to include events of clinical progression.

1.1 Synopsis: Overall Design	Added the following text (in bold) with regards to hormone level testing: ***Participants who discontinue due to clinical progression will be unblinded at the EOT visit but are NOT eligible for participation in the optional OLE phase.*** ***Participants who discontinue due to reasons other than disease progression will not be unblinded and will not be eligible for participation in the optional OLE phase of the study.***	Added text to enable participants with clinical progression to be unblinded at the end of treatment visit to inform future treatment decisions consistent with FDA guidance (Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products Guidance for Industry [August 2019]). To minimize the potential for bias in the assessment of clinical progression, participants discontinuing study treatment with clinical progression will not be eligible to participate in the OLE phase of the study.

1.1 Synopsis: Treatment Groups and Duration	Removed the following text: *Participants will remain in the double-blind phase until death, disease progression ~~(as determined by Central Imaging Review using RECIST v1.1)~~, they prematurely discontinue study treatment for any reason, the study is stopped by the sponsor for any reason, or the required number of PFS events have been observed and the primary PFS analysis has been completed (based on current statistical assumptions, this is anticipated to be approximately 2 years after the first participant is randomized).* *Participants will remain in the OLE phase until death, disease progression ~~(as determined by Central Imaging Review using RECIST v1.1)~~, they prematurely discontinue study treatment for any reason, the study is stopped by the sponsor for any reason, participant qualifies for Sponsor's Continued Access Plan, or nirogacestat is commercially available*	Removed text to address discontinuations due to radiographic or clinical progression.
1.2 Schema	*Added the following footnote:* ***[2]Participants discontinuing study treatment due to clinical progression are not eligible for participation in the OLE.***	Added footnote to clarify participants discontinuing study due to clinical progression will not be eligible for participation in the OLE.

1.3.1 Double-Blind Phase SoA	Revised the following footnotes (added text in bold font): *25. AEs/SAEs: Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail.* ***Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).*** *26. Every 3 cycles and on: Following Cycle 7 Day 1, participants will return every 3 cycles for study visits until death, progressive disease ~~(as determined by Central Imaging Review using RECIST v1.1)~~, discontinuation of study treatment for any reason, study is stopped by the sponsor for any reason, or required number of PFS events have been observed and primary PFS analysis has been completed.*	Revised footnotes for consistency with revisions to the definition of PFS and to clarify a minimum follow-up timeframe for events of POI.
1.3.2 Open-Label Extension Phase SoA	Revised the following footnotes (added text in bold font): 19. *AEs/SAEs: Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail.* ***Females reporting AEs/AESIs/SAEs of POI and/or amenorrhea will have hormone levels assessed every three months until event resolution (or for at least 90 days after discontinuing study treatment).***	Revised to clarify a minimum follow-up timeframe for events of POI.

4.1.1 Overall Design for the Double-Blind Phase	Added the following text (bold font): • ***The investigator determines the participant to have clinical progression which occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status;[2]*** ***[2]If a participant has clinical progression; the participant will return to the site for an end of treatment (EOT) visit within 14 days of the date of clinical progression. During the EOT visit, the participant will be unblinded; however, the participant will NOT be eligible to enter the optional OLE phase.***	Added language to include clinical progression as a reason for study discontinuation.
4.1.2 Overall Design for the Optional Open-Label Phase	Added the following text (bold font): • ***The investigator determines the participant to have clinical progression which occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status***;	Added language to include clinical progression as a reason for study discontinuation.

4.2 Scientific Rationale for Study Design	Added the following text (bold font): ***Given the unique characteristics of DT/AF, applying RECIST v1.1 alone is not always an adequate means of capturing the entirety of the disease progression and its clinical impact on participants. In particular, DT/AF tumors have been shown to grow in an asymmetric nature that can infiltrate multiple layers of fascia, neurovascular bundles and complex joint spaces (Gounder, 2017; Villalobos, 2017). This asymmetric growth also impacts the plane in which RECIST v1.1 measurements are performed such that the plane selected for review at the beginning of the study may not match the plane which ultimately shows progressive disease. To address the complexities of evaluating DT/AF lesions, progression will be determined both radiographically using Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1 (Eisenhauer, 2009; Section 10.8) and clinically as assessed by the investigator.***	Added language to clarify the rationale for including clinical progression as part of the overall definition of disease progression.

6.1 Table 2	Added the following text (bold font) to the ingredient list for nirogacestat: ***Uncoated Tablets****:* *PF-03084014-04;* *Microcrystalline Cellulose;* *Lactose Monohydrate;* *Sodium Starch Glycolate; and* *Magnesium Stearate.* ***Opadry® QX Film Coated Tablets:*** ***Macrogol (PEG) Polyvinyl Alcohol Graft Copolymer,*** ***Talc,*** ***Titanium Dioxide,*** ***GMCC Type 1,*** ***Polyvinyl Alcohol – Part Hydrolyzed,*** ***Yellow #6 / Sunset Yellow FCF Aluminum Lake,*** ***Iron Oxide Yellow*** Added the following footnote to Table 2: ***1 Nirogacestat tablets may be uncoated or coated with a non-functional aqueous film coat (Opadry® QX) in the OLE phase of the study. In the double-blinded phase of the study, nirogacestat will only be dispensed in an uncoated tablet.***	Updated the ingredient list for nirogacestat to include ingredients in the film coated tablet formulation which may be used in the OLE phase of the study. Added a footnote to clarify the use of this tablet formulation in the OLE phase of the study.
6.1.1 Double-Blind Phase Dosing Administration AND 6.1.2 Open-Label Phase Dosing Administration	Added the following text (bold font): ***To minimize time required onsite, the observation period may be shortened to 2 hours temporarily during a public health emergency (e.g. COVID-19) with prior medical monitor / sponsor approval.***	Added language to address temporary protocol modifications to address public health emergencies such as COVID-19.

6.2 Preparation/ Handling/Storage/ Accountability	Added the following text (bold font): ***Study treatment should be dispensed at the study site; however, direct to participant (DTP) shipping may be allowed with advance approval from the Sponsor in the event of a public health crisis such as COVID-19. Direct to participant shipping is not allowed at the C1D1 visit in the double blind or OLE phase of the study.***	Added language to address temporary protocol modifications to address public health emergencies such as COVID-19.
6.3.2 Blinding	Revised the following text (added text in bold font): ***Study participants who discontinue due to clinical progression will NOT be eligible to enroll into the optional OLE phase of the study.*** *If a participant discontinues study treatment for any reason other than progressive disease* ***~~(as determined by Central Imaging Review using RECIST v1.1.)~~,*** *the study treatment allocation will not be unblinded.*	Revised text to enable participants with clinical progression to be unblinded at the end of treatment visit to inform future treatment decisions.

6.3.2.1 Breaking the Blind	Added the following text (bold font): ***3. Clinical Progression: The investigator determines the participant needs to be withdrawn from the study to start emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status.*** ***• Prior to unblinding in this situation, the following criteria must be met:*** ***o All double-blind EOT study assessments have been completed in a blinded manner (refer to SoA table Section 1.3.1 for complete list of assessments).*** ***o All ongoing AEs/SAEs from the double-blind phase have been assessed for causality by the investigator or qualified designee in a blinded manner and recorded in the eCRF.*** ***o Sponsor designee has confirmed that the criteria above have been met and only then will the IRT allow the study treatment to be unblinded.***	Added text to enable participants with clinical progression to be unblinded at the end of treatment visit to inform future treatment decisions.
6.7.3 Exclusion Criteria - Open-Label Extension Phase	Added the following text (bold font): ***4. Participant has initiated a new treatment for DT/AF including tyrosine kinase inhibitors, other antineoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy or other antibodies; and/or any investigational treatment for DT/AF after the Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1).***	Added exclusion criteria to ensure participants continuing into the OLE Phase of the study have not initiated a new treatment for DT/AF prior to enrollment in the OLE phase of the study.

7.1 Discontinuation of Study Treatment	Revised the following text (added text in bold font): • ***The investigator determines the participant to have clinical progression which occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status***; • *Participant's study treatment is unblinded for safety reasons or any reason other than progressive disease ~~(as determined by Central Imaging Review)~~ (Section 6.3.2.1);*	Revised language to include clinical progression as a reason for study discontinuation.

8 Study Assessments and Procedures	Added the following text (bold font): • ***In the event that a study site or participant is unable to complete a study visit or procedure due to restrictions caused by a public health emergency such as COVID-19, the following accommodations may be allowed temporarily with prior approval from the medical monitor / sponsor. Any deviations from the study protocol due to a public health emergency should be documented in the source data and eCRF.*** ***o If a study participant cannot attend a study visit onsite due to a public health emergency, they may be able to attend a local hospital/clinic or arrange for a telehealth or home healthcare visit.*** ***o Clinical laboratory assessments may be performed locally, as required.*** ***o Electrocardiograms may be performed locally. Every effort should be made to perform ECGs in triplicate; however, a single ECG will be allowed if necessary due to a public health emergency.*** ***o Study imaging including CT and/or MRI should be performed per the schedule in the SoA at a qualified imaging facility; however, local imaging may be allowed with prior sponsor approval.***	Added language to address temporary protocol modifications to address public health emergencies such as COVID-19.

8 Study Assessments and Procedures EOT Visit Double Blind Phase Table 6	Revised text as follows (added text in bold font): ~~1. Central Imaging Review determines~~ A participant has **met the study endpoint of radiographic progression** using RECIST v1.1 (**determined** by Central Imaging Review) **or clinical progression as assessed by the investigator;** ***If the Investigator determines the participant has clinical progression, the following steps will occur:*** ***1. Participant will return to the site for an EOT visit as soon as possible but no later than 14 days of the date of the clinical progression.*** ***2. Participant should be instructed to remain on study treatment until the EOT visit (if possible).*** ***3. All double-blind EOT study assessments will be completed in a blinded manner (refer to SoA table Section 1.3.1 for complete list of assessments).*** ***4. All ongoing AEs/SAEs from the double-blind phase will be assessed for causality by the investigator (or qualified designee) in a blinded manner and recorded in the eCRF.*** ***5. Sponsor designee will confirm that the above criteria have been met. Only then will the IRT allow the participant's study treatment assignment to be unblinded.*** ***6. Participants discontinuing due to clinical progression are NOT eligible to participate in the OLE phase of the study.*** If a participant discontinues study treatment for any reason other than progressive disease ~~as determined by Central Imaging Review~~	Added language to include clinical progression as a reason for study treatment discontinuation.

	~~using RECIST v1.1.)~~ the following steps will occur:	
8 Study Assessments and Procedures EOT Visit OLE Phase Table 7	Revised text as follows (added text in bold font): ~~1. Central Imaging Review determines~~ A participant has **met the study endpoint of radiographic progression** using RECIST v1.1 (**determined** by Central Imaging Review) **or clinical progression as assessed by the investigator;** • ~~Central Imaging Review determines that a participant has progressive disease (using RECIST v1.1);~~	Revised language to include clinical progression as a reason for study treatment discontinuation.
8.1.2 Clinical Progression	Added the following text (bold font): ***Clinical progression occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status.*** ***The date and reason for clinical progression will be documented in the eCRF. Study participants who discontinue due to clinical progression will be unblinded at the EOT visit but will NOT be eligible for participation in the optional OLE phase.***	Added language to include clinical progression as part of the overall definition of disease progression.
8.3.6 Adverse Events of Special Interest	Added the following text (bold font): ***[1] Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).***	Added text to clarify a minimum follow-up timeframe for events of POI.

8.5 Pharmacokinetics	Added the following text (bold font): • ***To minimize the amount of time a participant is required to remain onsite during a public health emergency such as COVID-19, the 3-hour C1D1 PK sample may be omitted with prior medical monitor / sponsor approval.***	Added language to address temporary protocol modifications to address public health emergencies such as COVID-19.
9.4 Statistics	Revised text as follows (added text in bold font): ***In addition, strategies on dealing with protocol deviations due to COVID-19 will be detailed in the SAP.*** *Progression will be* ***determined radiographically*** ~~*assessed*~~ *by independent, blinded Central Imaging Review using RECIST v1.1 (Eisenhauer, 2009)* ***as described in Section 8.1.1 or clinically by the investigator as defined and described in Section 8.1.2.*** *All data collected after crossover to nirogacestat (for participants who were previously randomized to placebo in the double-blind phase and receive nirogacestat in the OLE phase after* ***radiographic*** *disease progression) will be analyzed and reported separately.*	Added language to address temporary protocol modifications to address public health emergencies such as COVID-19. Revised language to account for clinical progression as part of the overall definition of disease progression. Added "radiographic" for clarity as only participants with radiographic progression are eligible for participation in the OLE phase of the study.

10.2 Appendix 2: Clinical Laboratory Tests	Added the following text (bold font): ***In the event of a public health emergency, clinical laboratory assessments may be performed locally (with prior medical monitor / sponsor approval) with results and local laboratory normal values entered into the eCRF.*** Table 12: Footnote 6 ***Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).***	Added language to address temporary protocol modifications to address public health emergencies such as COVID-19. Added text to clarify a minimum follow-up timeframe for events of POI.
ADMINISTRATIVE CHANGES AND CLARIFICATIONS		
Section # and Name	**Description of Change**	**Brief Rationale**
Title Page and Appendix 10.10.1 List of Contacts for Study	Changed the SpringWorks corporate address from: SpringWorks Therapeutics 575 5th Avenue New York, NY 10017 To: SpringWorks Therapeutics 100 Washington Blvd Stamford, CT 06902	Updated the corporate address to reflect the new SpringWorks corporate address.
Sponsor Signatory	Replaced Julie Wolfson with Jun Liu, PhD as the Statistics signatory. Updated title for Nicole Leedom to **Senior** Director, Clinical Operations.	Updated for administrative purposes.
Throughout protocol	Corrected minor grammatical and typographical errors.	Updated for editorial purposes.
Throughout protocol	Replaced mention of United BioSource LLC (UBC) with “Safety” and SpringWorksPV@ubc.com with “PV@springworkstx.com.”	Updated for administrative purposes.
Throughout protocol	“Radiographic” was added throughout the protocol when reference is made to “progressive disease using RECIST v1.1.”	Added text to distinguish between radiographic and clinical progression.

4.1.1 Overall Design for the Double-Blind Phase	Updated footnote numbering. Added the following text to footnote 1 (added text in bold): *[1]If Central Imaging Review determines that a participant has **radiographic** progressive disease (using RECIST v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will return to the site for an end of treatment (EOT) visit within 14 days of the notification **from the central imaging core laboratory**. During the EOT visit, the participant will be unblinded and have the option to enter the OLE phase if eligible (Section 6.7.1).*	Updated for clarity.
8.3.6 Adverse Events of Special Interest	Added the following text in bold text: *Non-serious AESIs must be reported to the sponsor (by entering the AESI into the eCRF **and submitting a paper SAE/AESI report form to Safety**) as soon as possible, but no later than 5 business days of awareness.*	Updated to clarify process for documenting AESIs.
10.8 Appendix 8 RECIST	Revised the following test (added text in bold font): • *Target Lesion - ~~--all measurable lesions up to maximum of 2 lesions per organ,~~ **The investigator will select up to** 5 **target** lesions in total, representative of all involved organs **at Baseline.**~~, should be identified as target lesions at baseline by the investigator.~~*	Revised text for consistency with Section 6.3.1 of the Protocol which was updated with Protocol Amendment 2.
10.9 Appendix 9 Abbreviations	Updated abbreviation list to include: DTP – direct to participant POI – primary ovarian insufficiency And remove: UBC – United BioSource LLC	Updated for administrative purposes.

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Protocol: NIR-DT-301

Amendment 5 Summary and Rationale

Date of Amendment: 09 Feb 2021

This amendment is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Apart from minor edits, formatting changes and necessary editorial updates, the following changes were made to the protocol amendment 4 (07 July 2020):

Rationale for the Amendment:

SUBSTANTIAL CHANGES		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis Objectives and Endpoints AND 3 Objectives and Endpoints (Table 1)	Made the following revisions to the definition of disease progression in the primary endpoint (added text in bold font below): *PFS defined as the time from randomization until the date of assessment of progression or death by any cause will be determined.* *Progression will be determined radiographically using Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1 (Eisenhauer, 2009; Section 10.8) or clinically as assessed by the investigator.* ~~*Clinical progression occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status.*~~ ***Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.***	Given the unique characteristics of DT/AF including its ability to grow in an asymmetric manner, applying RECIST v1.1 alone is not adequate in capturing the entirety of disease progression and its clinical impact on participants. To account for this limitation, the definition of disease progression in the primary endpoint was updated to include qualified events of clinical progression.
1.1 Synopsis Objectives and Endpoints AND 3 Objectives and Endpoints (Table 1)	Added the following text (in bold): *Overall response rate, defined as the proportion of participants with CR + PR assessed* ***via central reader using*** ~~*by*~~ ***RECIST*** *v1.1 Criteria;*	Text added to clarify the secondary endpoint of overall response rate will be evaluated using central review of RECIST as opposed to local review of RECIST.

1.1 Synopsis: Overall Design	Made the following revisions (added text in bold font below): *Participants who discontinue due to reasons other than **radiographic** disease progression **as determined via central review** will not be unblinded and will not be eligible for participation in the optional OLE phase of the study.*	Added text to clarify only participants who discontinue due to radiographic progression will be eligible for unblinding and participation in the OLE.
1.3.1 Double-Blind Phase SoA	Added a line item for "Local RECIST v1.1 read" at all scheduled measurements for RECIST and revised the following footnote (added text in bold font): *20. Tumor measurement using RECIST v1.1 assessment (Section 8.1.1.2): CT scans (contrast required unless contraindicated) or MRI scans (no contrast required) will be acquired to assess tumor changes. The modality (CT or MRI) for tumor assessment is to be determined by the investigator. The imaging modality used to assess the tumor at screening must be used at each subsequent visit. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review, but participant enrollment is not dependent on central review. **Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.*** Adjusted the ConMed review line item through 30 days after the last dose of study treatment.	Added local review of RECIST for comparison with central review of RECIST. Adjusted the ConMed review line item through 30 days after the last dose of study treatment to align with the collection of concomitant medications between EOT and FUP.

1.3.2 Open-Label Extension Phase SoA	Added a line item for "Local RECIST v1.1 read" at all scheduled measurements for RECIST and revised the following footnote (added text in bold font): *15. Tumor imaging: CT (contrast required unless contraindicated) or MRI (no contrast required) using RECIST v1.1 (modality to be determined by the investigator) is required. Whichever imaging modality is used to measure the tumor by RECIST v1.1 at screening in the double-blind phase must be used at each subsequent visit throughout the OLE phase. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review.* ***Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.*** Adjusted the ConMed review line item through 30 days after the last dose of study treatment.	Added local review of RECIST for comparison with central review of RECIST. Adjusted the ConMed review line item through 30 days after the last dose of study treatment to align with the collection of concomitant medications between EOT and FUP.
3. Objectives and Endpoints Table 1	Added the following text (bold font): Exploratory Objective: **To perform exposure-response analysis using a final population PK/PD (PopPK/PD) model.** Exploratory Endpoint: **To determine the relationship between exposure and primary, secondary, and/or exploratory efficacy and safety endpoints.**	Added an exploratory objective to perform exposure-response analysis using a PopPK/PD model to determine the relationship between exposure and primary, secondary, and/or exploratory efficacy and safety endpoints.

4.1.1 Overall Design for the Double-Blind Phase	Revised the following text (new text in bold font): *The investigator determines the participant ~~to have~~* ***is experiencing*** *clinical progression which ~~occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status~~* ***is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF;[2]*** *[2]If a participant has clinical progression* ***as determined by the investigator;*** *the participant will return to the site for an end of treatment (EOT) visit within 14 days of the date of clinical progression. During the EOT visit, the participant will* ***NOT*** *be unblinded; ~~however, the participant~~* ***and*** *will NOT be eligible to enter the optional OLE phase.*	Clarified the definition of clinical progression for consistency with rest of protocol. Also, clarified participants who discontinue due to clinical progression will not be unblinded or eligible to participate in the OLE phase of the study.

4.1.2 Overall Design for the Optional OLE Phase	Revised the following text (new text in bold font): *The investigator determines the participant to have clinical progression* ***which is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.*** ~~*which occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status;*~~	Clarified the definition of clinical progression for consistency with rest of protocol.

6.3.2 Blinding	Revised text as follows (added text in bold font): *Study participants who discontinue due to clinical progression will* ***NOT be unblinded and will*** *NOT be eligible to enroll into the optional OLE phase of the study.* ***These participants should be discontinued from the study after completing an EOT and FUP visit as specified in applicable SoA table.*** *If a participant discontinues study treatment for any reason other than* ***radiographic*** *progressive disease* ***as determined via central review****, the study treatment allocation will not be unblinded.* *3. ~~Clinical Progression: The investigator determines the participant needs to be withdrawn from the study to start emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status.~~* *• ~~Prior to unblinding in this situation, the following criteria must be met:~~* *o ~~All double-blind EOT study assessments have been completed in a blinded manner (refer to SoA table Section 1.3.1 for complete list of assessments).~~* *o ~~All ongoing AEs/SAEs from the double-blind phase have been assessed for causality by the investigator or qualified designee in a blinded manner and recorded in the eCRF.~~* *o ~~Sponsor designee has confirmed that the criteria above have been met and only then will the IRT allow the study treatment to be unblinded.~~*	Updated language to clarify participants discontinuing due to clinical progression will remain blinded to treatment assignment. In an effort to minimize bias in the discontinuation of participants due to events of clinical progression, participants discontinuing due to clinical progression will not be unblinded or eligible to participate in the OLE phase of the study.

6.5.1 Concomitant Medications and/or Procedures	Revised text as follows (added text in bold font): *6.5.1 ~~Prior~~ Concomitant Medications and/or Procedures* *Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of informed consent and/or receives during the study* ***through 30 days after the last dose of study treatment must be recorded along with****:*	Added text to clarify concomitant medications / procedures should be reported within 30 days after the last dose of study treatment.
6.5.1.2 Excluded / Restricted Concomitant Medications and / or Procedures and Table 3	Revised text as follows (added text in bold font): *Table 3 describes the concomitant medications and/or procedures that are excluded/restricted prior and/or throughout the duration of the study* ***until the termination of study treatment****. Contact the medical monitor/sponsor with any questions regarding excluded/restricted medications.* Similar text was also added throughout Table 3 and in the footnotes.	Added text to clarify excluded/restricted medications and/or procedures are restricted during the treatment phase.

7.1 Discontinuation of Study Treatment	Revised text as follows (added text in bold font): *The investigator determines the participant ~~to have~~* ***is experiencing*** *clinical progression which* ***is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.*** *~~occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status;~~* *Participant's study treatment is unblinded for safety reasons or any reason other than* ***radiographic*** *progressive disease* ***as determined via central review*** *(Section 6.3.2.1);*	Updated language to clarify participants discontinuing due to clinical progression will remain blinded to treatment assignment.

8. Study Assessments and Procedures	Revised text as follows (added text in bold font): • *In the event that a study site or participant is unable to complete a study visit or procedure due to restrictions caused by a public health emergency such as COVID-19, the following accommodations may be allowed temporarily with prior approval from the medical monitor / sponsor. Any deviations from the study protocol due to a public health emergency should be documented in the source data and eCRF* ***and reported to the IRB/EC in accordance with their reporting requirements****.* *o* ***Clinical laboratory assessments may be performed locally with results and local laboratory normal values entered into the eCRF.*** *o* ~~*Clinical laboratory assessments may be performed locally, as required.*~~ *o Electrocardiograms may be performed locally.* ***If ECGs are performed locally, ECG tracings should be collected and the investigator (or designee) assessment should be documented.*** *Every effort should be made to perform ECGs in triplicate; however, a single ECG will be allowed if necessary due to a public health emergency.* *o Study imaging including CT and/or MRI should be performed per the schedule in the SoA at a qualified imaging facility; however, local imaging may be allowed with prior sponsor approval.* ***Local imaging will need to be uploaded for Central Imaging Review.***	Added language to clarify recommendations for study assessments in the event of a public health emergency such as COVID-19.

Section 8 Table 6 EOT	Revised text as follows (added text in bold font): ~~*If the investigator determines the participant has clinical progression, the following steps will occur:*~~ ~~*1. Participant will return to the site for an EOT visit as soon as possible but no later than 14 days of the date of the clinical progression.*~~ ~~*2. Participant should be instructed to remain on study treatment until the EOT visit (if possible).*~~ ~~*3. All double-blind EOT study assessments will be completed in a blinded manner (refer to SoA table Section 1.3.1 for complete list of assessments).*~~ ~~*4. All ongoing AEs/SAEs from the double-blind phase will be assessed for causality by the investigator (or qualified designee) in a blinded manner and recorded in the eCRF.*~~ ~~*5. Sponsor designee will confirm that the above criteria have been met. Only then will the IRT allow the participant's study treatment assignment to be unblinded.*~~ ~~*6. Participants discontinuing due to clinical progression are NOT eligible to participate in the OLE phase of the study.*~~ *If a participant discontinues study treatment for any reason other than* ***radiographic*** *progressive disease* ***as determined via central review*** *the following steps will occur:*	Removed duplicate text as scenario for discontinuations due to reasons other than radiographic progressive disease are already covered.
Section 8 Table 7 EOT	Revised text as follows (added text in bold font): ***The investigator determines that the participant is experiencing clinical progression defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF;***	Added clinical progression as a reason for end of treatment in the OLE phase of the study.

Section 8.1.1 Tumor Imaging On Study Scans	Revised text as follows (added text in bold font): ***Study imaging including MRI and/or CT should be performed per the schedule in the SoA at a qualified imaging facility; however, in the event that a study site or participant is unable to complete a study visit or procedure due to restrictions caused by a public health emergency such as COVID-19, local imaging may be allowed with prior sponsor approval.***	Added language to clarify requirements for local imaging in the event of a public health emergency.
Section 8.1.1.2 Tumor Assessment Using RECIST Version 1.1 Criteria	Revised text as follows (added text in bold font): *Tumor assessment for primary and secondary endpoints (PFS and ORR, respectively) as measured by CT (contrast required unless contraindicated) or MRI (no contrast required), will be evaluated by Central Imaging Review* ***for all participants*** *using RECIST v1.1 (Eisenhauer, 2009) at the following timepoints:* ***While tumor assessments performed by Central Imaging Review will be used for primary and secondary endpoints, tumor measurements will also be performed locally using RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet as specified in the SoA (Sections 1.3.1 and 1.3.2) and whenever disease progression is suspected (e.g., symptomatic deterioration).***	Added language to include collection of local reads of RECIST.

8.1.2. Definition and Assessment of Clinical Progression	Revised text as follows (added text in bold font): ***Clinical*** *progression* ***is*** *defined as* ***the onset or worsening of symptoms resulting in a global deterioration of health status causing*** *the permanent discontinuation from study treatment and the initiation of emergent treatment (****e.g.****, radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.* ***The date of clinical progression will be the earliest date of onset or worsening of symptoms resulting in a global deterioration of health status. In addition, AEs and SAEs associated with clinical progression and concomitant medications and procedures initiated for the treatment of DT/AF within 30 days of the last dose of study treatment will be documented in the eCRF. A clinical progression narrative will also be developed by the PI for events of clinical progression which will be documented in EDC and include a description of onset or worsening of symptoms resulting in a global deterioration of health status, the location of progressing lesions, and evidence of vital structure involvement (as reported by the PI), as applicable.*** ***When disease progression is suspected (e.g., symptomatic deterioration), imaging should be performed and submitted to the central imaging core laboratory for Central Imaging Review. If progressive disease is not determined radiologically via central review of RECIST v1.1 per Section 8.1.1.2, but the participant meets the definition of clinical progression, the participant may be discontinued for clinical progression. Study participants who discontinue due to clinical progression will NOT be unblinded at the EOT visit and will NOT be eligible for participation in the optional OLE phase.*** ***Imaging data from participants who discontinue due to clinical progression will be evaluated for changes in tumor characteristics or involvement of vital organ structure at the site of progression, which may include:***	Added language to describe definition and assessment of events of clinical progression.

	1. Individual tumor measurements including all available planes of measurement ***2. Volumetric MRI, if available*** ***3. T2 hyperintensity, if available*** ***Events of clinical progression will be adjudicated by an independent blinded central clinical review committee which will qualify events of clinical progression for inclusion in the primary analysis of PFS prior to study unblinding according to a Central Clinical Review Charter.***	
8.2.5. Clinical Safety Laboratory Assessments	Added text throughout table as follows (added text in bold font): ***In the event of a public health emergency, clinical laboratory assessments may be performed locally with results and local laboratory normal values entered into the eCRF.***	Added language to clarify requirements for local laboratory assessments in the event of a public health emergency.
9.4.1 Efficacy Analyses	Revised text as follows (added text in bold font): Primary Endpoint: *The primary efficacy endpoint is PFS, which is defined as the time from randomization until the date of assessment of progression or death by any cause (whichever occurs first). Progression will be determined radiographically by independent, blinded Central Imaging Review using RECIST v1.1 (Eisenhauer, 2009) as described in Section 8.1.1 or clinically by* ***an*** *investigator* ***whose assessment is qualified via independent blinded central clinical review*** *as ~~defined and~~ described in Section 8.1.2. Participants who have not progressed or died will be censored at the date of the last response assessment. Participants who do not have any response assessments will be censored at the date of randomization. Sensitivity analysis utilizing alternative censoring methods will be described in the SAP.* Secondary Endpoint: *Overall response rate, defined as the proportion of participants with CR + PR assessed* ***via central reader using ~~by~~ RECIST v1.1;***	Added language to clarify only qualifying events as determined via independent blinded central clinical review will be included in the primary analysis of PFS. Also clarified the overall response rate will be determined via central review.

ADMINISTRATIVE CHANGES AND CLARIFICATIONS		
Section # and Name	**Description of Change**	**Brief Rationale**
Throughout protocol	Corrected minor grammatical and typographical errors. Defined abbreviations at first use.	Updated for editorial purposes.
6.2 Preparation/Handling / Storage / Accountability	Revised text as follows (added text in bold font): *Further guidance and information about the **handling, storage, and** final disposition of unused study treatment (bottles/tablets) are provided in the pharmacy manual.*	Updated for clarity.
Section 8 Table 6 and Table 7	Added text throughout table as follows (added text in bold font): ***The scan(s) conducted at the screening visit should also be read locally.*** ***Scans should also be read locally per RECIST v1.1.***	Updated for clarity.
Section 9.4.3 Other Analyses	Revised as follows (added text in bold font): ***Sensitivity analyses, pharmacokinetic, pharmacodynamic**, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.*	Updated for clarity.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Revised as follows: *In the event of a public health emergency, clinical laboratory assessments may be performed locally ~~(with prior medical monitor / sponsor approval)~~ with results and local laboratory normal values entered into the eCRF.*	Updated for clarity.
10.9 Appendix 9 Abbreviations	Updated abbreviation list to include: PopPK - Population pharmacokinetic	Updated for administrative purposes.

STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)

Protocol Number:	NIR-DT-301
Protocol Version and Date:	Amendment 5: 09 February 2021 Amendment 4: 07 July 2020 (not released to sites) Amendment 3: 27 January 2020 Amendment 2: 14 October 2019 Amendment 1: 09 July 2019 Original: 03 August 2018
Name of Test Drug:	Nirogacestat
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Placebo-Controlled
Sponsor:	SpringWorks Therapeutics 100 Washington Blvd. Stamford, CT 06902 United States
Sponsor Representative:	[redacted] Sponsor Biostatistician
Analysis Plan Date:	07 April 2022
Analysis Plan Version:	Final Version 1.0

Author:

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Date

Sponsor Signatory

[redacted]
SpringWorks Therapeutics, Inc

Date

[redacted]
SpringWorks Therapeutics, Inc

Date

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
APC	Adenomatous polyposis coli
BOR	Best Overall Response
BPI	Brief Pain Inventory
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double-blind
DOR	Duration of response
DT/AF	Desmoid Tumors/Aggressive Fibromatosis
DTIS	Desmoid Tumor Symptom Scale
DTSS	Desmoid Tumor Impact Scale
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
FAP	Familial adenomatous polyposis
FUP	Follow-up
GODDESS	GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale
HR	Hazard ratio
IRT	Interactive response technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
OD	Ovarian dysfunction
OLE	Open-label extension
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

Abbreviation	Definition
PK	Pharmacokinetic
PP	Per-Protocol
PR	Partial response
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System Physical Function
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	International System of Units
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This document is the statistical analysis plan (SAP) for NIR-DT-301, a Phase 3, randomized, double-blind, placebo-controlled study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF). It is based on Protocol Amendment 5, dated 09 February 2021. The safety and efficacy for the double-blind phase of NIR-DT-301 will be discussed in two parts:

1. The main body of the SAP (Main SAP) will detail the statistical analyses to be conducted using clinical data for the primary analysis data cut after approximately 51 events have occurred and a final double-blind phase analysis after last-participant last visit (LPLV) for the double-blind phase of the study and

2. A patient-reported outcome (PRO) Addendum for analysis of PRO data.

As with the study's Main SAP, the PRO Addendum will be finalized before the unblinding of the clinical database once the target number of events have been observed. Analysis of pharmacokinetic (PK) data from samples collected during the study will be described in a separate PK SAP that documents the integrated PK analyses (including data from early phase studies) for nirogacestat. An End of open-label extension (OLE) SAP will be developed for the OLE phase data.

The primary analysis of safety, efficacy, and tolerability is planned after approximately 51 events have occurred in the double-blind phase of the study (primary analysis data cut). A clinical study report will be developed using the primary analysis data cut. A final analysis of the double-blind phase of the study will be performed after the last participant last visit has occurred for the double-blind phase of the study; this final analysis will inform safety and nominal p-values will be presented for efficacy endpoints, but no interpretation will be made on these results. Unless otherwise specified, the analysis covered by this document will include only clinical data collected during the double-blind (DB) phase of the study. The various SAP components for study NIR-DT-301 are summarized below:

SAP Component	Focus	SAP Completion Date
Main SAP	Analysis of safety and efficacy based on clinical data collected during the DB phase of the study including the primary analysis after approximately 51 events have occurred and end of double-blind phase analysis after (LPLV)	Prior to unblinding
PRO Addendum	Analysis of PRO data based on data collected during the DB phase of the study	Prior to unblinding
PK SAP	Integrated analysis of nirogacestat PK data, including PK samples collected in NIR-DT-301	Prior to unblinding
End of OLE SAP	Analyses for long-term outcomes based on clinical and PRO data collected during the DB and OLE phases of the study	Prior to the End of the OLE phase

1.1.2. Study Objectives

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The primary objective of this study is:

- To determine the efficacy (as defined by progression-free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF

The secondary objectives of this study are:

- To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of AEs
- To determine the Objective Response Rate (complete response [CR] + partial response [PR]) of nirogacestat in participants with progressing DT/AF
    - To describe the duration of response (DOR) and duration of stable disease (DOSD) when data is available
- To evaluate desmoid tumor symptoms and impacts using the following patient-reported outcomes (PROs):
    - GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS)
    - Brief Pain Inventory (BPI) short form
    - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30

The exploratory objectives of this study are:

- To compare tumor volume changes measured by magnetic resonance imaging (MRI) in participants with progressing DT/AF
- To evaluate desmoid tumor symptoms and impacts using the following PROs:
    - Patient Global Impression of Severity (PGIS)
    - Patient Global Impression of Change (PGIC)

- To perform genotyping for germline and somatic mutation in adenomatous polyposis coli (APC) and β-catenin genes (CTNNB1)
- To assess modulation of the Notch pathway by evaluating NOTCH response genes in tumor biopsies at screening and disease progression or end of treatment (EOT)
- To assess MRI T2 hyperintensity at baseline and post-drug administration
- To inform development of a population pharmacokinetic (PK) model of nirogacestat
- To perform exposure-response analysis using a final population PK/PD (PopPK/PD) model
- To evaluate the effect of nirogacestat on clinical events related to disease specific desmoid tumor co-morbidity

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. 142 eligible participants were randomized to study treatment (nirogacestat or placebo) in a 1:1 ratio. Randomization was stratified by primary tumor location (intra-abdominal or extra-abdominal).

This study will consist of 2 phases: the double-blind phase and the optional OLE phase. Refer to the schedule of activities (SoA Table 1 and Table 2) for details on assessments and timing of study visits.

Participants will be screened up to 28 days prior to the first dose of study treatment and eligibility will be based on inclusion and exclusion criteria provided in Section 5.1 and 5.2 of the protocol. Participants will be randomized to study treatment at Cycle 1 Day 1 using interactive response technology (IRT) and will orally administer 150 mg twice daily, continuously in 28-day cycles.

Following the baseline visit (Cycle 1 Day 1), the participants will return to the clinic for study visits at Cycle 1 (Days 8, 15, 22), Cycle 2 (Day 28), Cycle 4 (Day 1), and then on Day 1 of every 3 cycles thereafter.

1.2.2. Randomization Methodology

Randomization will be stratified based on the following tumor locations:

1. Intra-abdominal (include mesentery and pelvis)

   OR

2. Extra-abdominal (including head/neck, para-spinal, extremities, abdominal wall, chest wall, and other locations).

If the participant has multiple target tumors that are located both in the intra- and extra-abdominal location, the tumor should be classified as intra-abdominal.

1.2.3. Stopping Rules and Unblinding

For the double-blind phase, the participant, investigator, and all other clinical site personnel will be blinded to the assigned treatment allocation. All sponsor personnel will also be blinded except for the sponsor's quality assurance designee(s), safety designee(s), and clinical supply material designee(s).

If central imaging review determines that a participant has radiographic progressive disease (using Response Evaluation Criteria In Solid Tumors [RECIST] v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will then return for the EOT visit which will unblind the participant and participant will have the option to enter OLE phase, if eligible. All EOT assessments and all ongoing adverse events (AEs) / serious AEs (SAEs) must (1) be assessed for causality by the investigator or qualified designee in a blinded manner and (2) recorded in the electronic case report form (eCRF) prior to the unblinding of the study treatment allocation.

Study participants who discontinue due to clinical progression will NOT be unblinded and will NOT be eligible to enroll into the optional OLE phase of the study. These participants should be discontinued from the study after completing an EOT and follow-up (FUP) visit as specified in applicable SoA table.

If a participant discontinues study treatment for any reason other than radiographic progressive disease as determined via central review, the study treatment allocation will not be unblinded.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, are provided in Table 1 (for double-blind phase) and Table 2 (for OLE phase). Please note that references to specific sections and table numbers in the schedules (and the associated table footnotes) are referring to sections and tables within the study protocol.

Table 1. Schedule of Assessments (SoA) – Double-Blind Phase

Double-Blind Phase Cycle Number	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Week 13** *Day 85* *(± 7 days)*	**Week 25 & On** *Day 169 & On* *(± 7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Informed consent[2]	X									
I/E criteria	X	X								
Demography	X									
Medical history including menstrual history for women	X									
ECOG performance status[4]	X	X				X	X	X	X	X
Physical examination[5]	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X
Weight/height[7]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[8]	X	X[8a] *(pre-& post dose)*	X[8b] *(post dose)*			X	X	X	X	X
Laboratory										
Tumor biopsy[9]	X[9a]								X[9b] *(optional)*	
Blood for serology[10]	X									
Blood for serum pregnancy test (WOCBP only)[11]	X									
Blood for PK sampling[12]		X[12a] *(serial)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*		
Blood for pharmacogenomics[13]		X *(optional)*								
Blood for genotyping[14]		X								
Blood for safety labs[15]	X	X	X	X	X	X	X	X	X	X

Double-Blind Phase Cycle Number	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Week 13** *Day 85* *(± 7 days)*	**Week 25 & On** *Day 169 & On* *(± 7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Blood for female hormone levels[15]	X	X			X	X	X	X	X	X
Blood for male hormone levels[15]		X					X	X	X	X
Urinalysis[16]	X	X				X	X	X	X	X
Urine pregnancy test (WOCBP only)[17]		X			X	X	← *(monthly)[17a]* →		X	X
Patient-Reported Outcomes (PROs)[18]										
Home ePRO device training	X									
GODDESS (symptom scale)	← *(refer to Protocol Table 8)* →					← *(monthly assessment, refer to Protocol Table 8)* →				← *(refer to Protocol Table 8)* →
BPI short form										
PROMIS PF short form 10a plus 3 additional items from PROMIS item banks										
GODDESS (impact scale)										
EORTC QLQ-C30										
PGIS										
PGIC										
Imaging and RECIST										
Pre-Randomization RECIST v1.1 Calculation Worksheet[19]	X									
CT or MRI scan for tumor measurement (using RECIST v1.1)[20]	X[20a]						X[20b]	X[20b]	X[20c]	

Double-Blind Phase Cycle Number	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(±2 days)*	**Week 3** *Day 15* *(±2 days)*	**Week 4** *Day 22* *(±2 days)*	**Week 8** *Day 56* *(±2 days)*	**Week 13** *Day 85* *(±7 days)*	**Week 25 & On** *Day 169 & On* *(±7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
MRI scan for tumor volume assessment[20]	X							X[20b] *(every 6 cycles)*	X[20c]	
Local RECIST v1.1 read[20]	X[20a]						X	X[20b]	X[20c]	
Enrollment and Study Treatment										
Randomization[21]		X								
Study treatment dispensing[22]		X					X	X		
Study treatment administration/diary[23]		←	—	—	—	—	—	→		
Study treatment accountability							X	X	X	
Ongoing Monitoring										
Monthly wellness checks[24]	←	—	—	—	—	—	—	→		
ConMed review	←	—	—	—	—	—	—	—	—	→
AE/SAE review[25]	←	—	—	—	—	—	—	—	—	→

AE = adverse event; BID = twice daily; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = end of treatment; ePRO = electronic patient-reported outcome; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; ICF = informed consent form; I/E = inclusion/exclusion; IRT = interactive response technology; MRI = magnetic resonance imaging; OLE = open-label extension; PFS = progression free survival; PGIS = patient global impression of severity; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SoA = scheduled of activities; v = version; WOCBP = women of child bearing potential..

1. **Screening visit:** Assessments may occur up to 28 days prior to first dose of study treatment with a minimum screening period of 14 days to allow for participant completion of the screening and baseline PRO assessments (refer to Protocol Table 8 for PRO administration schedule). An extension to the screening period may be permitted on a case-by-case basis following discussion between the investigator and the medical monitor/sponsor. The reason(s) for the extension must be clearly documented.

2. **Informed consent process:** Includes participant signing the ICF and must be conducted prior to any study related procedures being performed. The date the participant signs the ICF will be Day 1 of the screening period. Refer to Protocol Section 10.1.3 for more detail on the ICF process.

3. **Baseline visit:** Assessments may be performed over a 48-hour period. All baseline assessments are to be conducted prior to first dose of study treatment except for the following assessments: post-dose 12-Lead ECGs and post-dose blood draws for pharmacokinetic (serial PK) sampling.
4. **ECOG performance status:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Protocol Section 10.7 for ECOG scale.
5. **Physical examination:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Protocol Section 8.2.2 for detail regarding physical examination requirements.
6. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature (following at least 5 minutes of rest). At baseline, assessment must be done prior to first dose of study treatment. Refer to Protocol Section 8.2.4 for more detail.
7. **Height:** Required at screening only. Weight to be collected at all visits.
8. **12-lead ECGs:** Will be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. Refer to Protocol Section 8.2.3 for more detail.

    8a. At baseline, triplicate ECGs are required at two timepoints: (1) prior to the first dose of study treatment and (2) approximately 1-hour post-dose.

    8b. At Cycle 1 Day 8, triplicate ECGs are required 1-hour (±10 minutes) post-dose.
9. **Tumor (core needle) biopsy:** If tumor biopsy and MRI are performed during the same study visit, the biopsy must be done after MRI. Refer to Protocol Section 8.1.3 and central laboratory manual for sample processing details.

    9a. At screening, tumor biopsy is only required if archival tissue is not available for study procedures. Tumor biopsy will be reviewed centrally to reconfirm diagnosis, but participant enrollment is not dependent on central review.

    9b. At EOT, tumor biopsy will be optional and additional pharmacogenomic consenting is required (Protocol Section 10.1.3).
10. **Serology:** Only required at screening and to include testing for hepatitis B virus (hepatitis B surface antigen), hepatitis C virus (hepatitis C antibody [Hepatitis C virus polymerase chain reaction, if hepatitis C antibody positive]), and human immunodeficiency virus. Refer to Protocol Section 10.2 and central laboratory manual for sample processing details.
11. **Serum pregnancy test:** Only required at screening for women of childbearing potential (WOCBP). Refer to Protocol Sections 8.3.5 and 10.4, and central laboratory manual for sample processing details.
12. **PK sampling:** Refer to Protocol Section 8.5 and Protocol Table 11, and central laboratory manual for sample processing details.

    12a. Serial PK: Required on Cycle 1 Day 1 at the following timepoints: pre-dose and 0.25-, 0.5-, 1-, 1.5-, 2- and 3-hours post-dose. All efforts will be made to obtain the sample within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing. Out of window PK draws will not be captured as deviations if the exact time of the sample collection is noted on the source documents and eCRF.

12b. Trough PK: The evening before applicable study visits, participants will record the exact time study treatment was taken in the eDiary using the home ePRO device. Participants will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.

13. **Pharmacogenomics:** Blood sample will be optional and additional pharmacogenomic consenting is required (Protocol Section 10.1.3). At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Protocol Sections 8.8 and 10.5, and central laboratory manual for sample processing details.

14. **Genotyping:** Required blood sample for all participants unless prohibited by local regulations. At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Protocol Section 8.7 and central laboratory manual for sample processing details.

15. **Safety Labs (hematology, serum chemistry, and hormone levels):** At baseline, must be done prior to first dose of study treatment. Refer to Protocol Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. The time of hormone level blood draws should also be recorded.

16. **Urinalysis:** At baseline, must be done prior to first dose of study treatment. Refer to Protocol Section 10.2 for a complete list of analytes and the central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results and only if blood or protein is abnormal.

17. **Urine pregnancy tests:** Only required for WOCBP. At baseline, urine pregnancy test must be done prior to first dose of study treatment to reconfirm eligibility. Refer to Protocol Sections 8.2.6 and 10.4 for more detail.

    17a. Following the Cycle 4 Day 1 study visit, all WOCBP participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to the study reference manual for additional details).

18. **PROs:** Participants will complete the questionnaires and record study treatment administration in the eDiary using a home ePRO device (Protocol Section 8.1.2). Refer to Protocol Table 8 for the PRO administration schedule.

19. **Pre-Randomization RECIST v1.1 Calculation Worksheet** (Protocol Section 8.1.1.1): As part of documenting that participants have satisfied inclusion criteria 2, sites are required to complete a worksheet (provided by the sponsor). The worksheet must be submitted to the sponsor's designee during the screening period as soon as the data are available to complete the worksheet. All worksheets must be received no later than 7 days prior to C1D1 to allow for review prior to randomization (refer to study reference manual for additional details).

20. **Tumor imaging:** All scans will be submitted to the central imaging core laboratory and read by Central Imaging Review throughout the study. Refer to Protocol Section 8.1.1 and imaging manuals for more detail.

    Tumor measurement using RECIST v1.1 assessment (Protocol Section 8.1.1.2): CT scans (contrast required unless contraindicated) or MRI scans (no contrast required) will be acquired to assess tumor changes. The modality (CT or MRI) for tumor assessment is to be determined by the investigator. The imaging modality used to assess the tumor at screening must be used at each subsequent visit. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review, but participant enrollment is not dependent on central review. Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.

Tumor volumetric assessment (Protocol Section 8.1.1.3)**:** MRI scans (no contrast required) will be acquired to assess tumor volume. All scans will be submitted to the central imaging core laboratory and assessed by Central Imaging Review.

If applicable, CT and MRI assessments may be conducted on the same day. However, MRI with no contrast must be performed prior to CT with contrast. MRI must be done prior to tumor biopsy if assessments occur on the same visit.

20a. Screening visit scans:

- MRI and CT scans obtained during the screening visit will serve as the participant's baseline scan for the study (CT scan only required if it is the chosen modality for RECIST v1.1 tumor measurement). Scans should be submitted to central imaging core laboratory as early in the screening period as possible to confirm scan quality is acceptable for analysis prior to randomization.
- Standard of care scan(s) acquired prior to the participant signing ICF may be used as the participant's screening visit scan(s) if obtained within 28 days of the first dose of study treatment and the quality of the scans are acceptable for analysis (as determined by the central imaging core laboratory). These scans will then be collected, stored, and documented as the screening visit scan(s). No other pre-enrollment images will be collected for central reading.

20b. On study treatment scans: Starting at cycle 4, MRI or CT scans for tumor assessment (RECIST v1.1) will be obtained every 3 cycles. Starting at cycle 7, MRI for tumor volume assessment will be obtained every 6 cycles.

20c. EOT visit scans: only required if not performed within the past 3 months.

21. **Randomization:** Participants will not be randomized to study treatment using IRT until all I/E criteria (Protocol Sections 5.1 and 5.2) have been confirmed and all pre-randomization baseline study assessments have been completed.

22. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles at applicable study visits.

23. **Study treatment administration/diary:** The first dose of study treatment (3 × 50 mg tablets) will be administered orally at the site at Cycle 1 Day 1 followed by a 3-hour observation period. Participants will administer study treatment at 150 mg (3 × 50 mg tablets) twice daily (BID) (approximately every 12 hours, without regard to food) continuously in 28-day cycles throughout the study. Participants should record daily administration of each study treatment dose in the eDiary using the home ePRO device. Refer to Protocol Section 6.1 for more detail.

24. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit). Refer to Protocol Section 8.2.7 for more detail.

25. **AEs/SAEs:** Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Refer to Protocol Section 8.3 for more detail. Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).

26. **Every 3 cycles and on:** Following Cycle 7 Day 1, participants will return every 3 cycles for study visits until death, progressive disease, discontinuation of study treatment for any reason, study is stopped by the sponsor for any reason, or required number of PFS events have been observed and primary PFS analysis has been completed.
27. **EOT visit:** EOT visit should be conducted prior to study treatment discontinuation to avoid a gap in study treatment for participants entering the OLE phase. All EOT assessments must be conducted prior to unblinding (if applicable refer to Protocol Section 6.3.2.1).

    If Central Imaging Review determines that a participant has progressive disease (using RECIST v1.1) the participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (but no later than 14 days of becoming aware of the progression).

    If the participant discontinues study treatment for any reason other than progressive disease (as determined by Central Imaging Review using RECIST v1.1), they will be encouraged to return to the site as soon as possible to complete the EOT visit assessments prior to study treatment discontinuation or as close as possible to the last dose of study treatment.
28. **Follow-up visit:** Only required for participants who are not continuing into the optional OLE phase and will occur 30 days (+7 days) after the last dose of study treatment.

Table 2. Schedule of Assessments (SoA) – Open-Label Extension Phase

OLE Phase **Cycle Number**	**Cycle 1[5]** *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2[5]**	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Cycle Day	**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Informed consent[1]	X								
I/E criteria[2]	X								
ECOG performance status[6]	*Same as double-blind EOT*				X	X	X	X	X
Physical examination[7]	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
Vital signs[8]	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
Weight	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
12-lead ECG[9]	X[9a] *(post dose)*	X[9b] *(post dose)*			X	X	X	X	X
Laboratory									
Blood for PK sampling[10]	X *(serial)*[10a]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]		
Blood for safety labs[11]	X[11a]	X	X	X	X	X	X	X	X
Blood for female hormone levels[11]	X[11a]			X	X	X	X	X	X

OLE Phase **Cycle Number**	**Cycle 1[5]** *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2[5]**	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Cycle Day	**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose* *(+ 7 days)*
Blood for male hormone levels[11]	X[11a]					X	X	X	X
Urinalysis[12]	*Same as double-blind EOT*				X	X	X	X	X
Urine pregnancy test (WOCBP only)[13]	*Same as double-blind EOT*			X	X	← *(Monthly)[13a]* →		X	X
Patient-Reported Outcomes (PROs)[14]									
GODDESS (symptom scale)					*(Monthly assessment, refer to Protocol Table 9)*		*(Quarterly assessment, refer to Protocol Table 9)*		*(Refer to Protocol Table 9)*
BPI short form									
PROMIS PF short form 10a plus 3 additional items from PROMIS item banks									
GODDESS (impact scale)									
EORTC QLQ-C30									
PGIS									
PGIC									
Imaging and RECIST									
CT or MRI scan for tumor measurement (using RECIST v1.1)[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	
Local RECIST v1.1 read[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	

OLE Phase **Cycle Number**	**Cycle 1[5]** *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2[5]**	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Cycle Day	**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Enrollment and Study Treatment									
Enrollment/first dose of open-label study treatment[4]	X								
Study treatment dispensing[16]	X					X	X		
Study treatment administration/diary[17]	←	—	—	—	—	—	→		
Study treatment accountability						X	X	X	
Ongoing Monitoring									
Monthly wellness checks[18]	←	—	—	—	—	—	→		
ConMed review	←	—	—	—	—	—	—	—	→
AE/SAE review[19]									

AE = adverse event; BID = twice daily; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = end of treatment; ePRO = electronic patient-reported outcome; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; ICF = informed consent form; I/E = inclusion/exclusion; IRT = interactive response technology; MRI = magnetic resonance imaging; OLE = open-label extension; PFS = progression free survival; PGIS = patient global impression of severity; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SoA = scheduled of activities; v = version; WOCBP = women of child bearing potential.

1. **Informed consent process:** Includes participant signing the ICF (exclusive to the OLE study phase) and must be conducted prior to administration of the first dose of open-label study treatment. Refer to Protocol Section 10.1.3 for more detail on the process.

2. **I/E criteria:** Exclusive to the OLE phase. Refer to Protocol Sections 6.7.2 and 6.7.3 for participant eligibility criteria specific to the OLE phase.

3. **Baseline visit:** The C1D1 visit of the OLE phase should be conducted on the same day as, or within 24 hours after, the double-blind EOT visit. A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1. All double-blind EOT visit assessments, as described in the double-blind SoA (Protocol Section 1.3.1), will be conducted **prior** to unblinding the participant's study treatment and prior to administration of the first dose of open-label study treatment.

4. **Enrollment and first dose of open-label study treatment:** Participants will be enrolled in the OLE phase using the IRT only after (1) all ongoing AEs/SAEs from the double-blind phase have been assessed for causality in a blinded manner by the investigator or qualified designee, and (2) all AE/SAE causality assessments have been entered into the eCRF. All double-blind EOT visit assessments must be completed **prior** to unblinding and taking first dose of open-label study treatment.

   Participants who were randomized to receive placebo in the double-blind phase will receive their first dose of study treatment at the site followed by a 3-hour observation period.

   Participants who were randomized to nirogacestat in the double-blind phase may take their first dose of open-label study treatment at home (observation period is not required).

5. **Study visits at Cycle 1 (Day 8, 15 and 22) and Cycle 2 (Day 28):** Only applicable for participants who were previously randomized to receive placebo in the double-blind phase. If a participant was randomized to receive nirogacestat in the double-blind phase, these study visits will not be conducted, and the participant will not be required to return to the site until Cycle 4 Day 1 visit.

6. **ECOG performance status:** Refer to Protocol Section 10.7 for the ECOG scale.

7. **Physical examination:** Refer to Protocol Section 8.2.2 for more detail regarding physical examination requirements.

8. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature (following at least 5 minutes of rest). Refer to Protocol Section 8.2.4 for more detail.

9. **12-lead ECGs:** Will be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. Refer to Protocol Section 8.2.3 for more detail.

   9a. At baseline, triplicate ECGs are required approximately 1-hour post-dose (open-label study treatment). Applicable only to participants who were previously randomized to receive placebo in the double-blind study phase.

   9b. At Cycle 1 Day 8 visit, triplicate ECGs are required 1-hour (±10 minutes) post-dose. Applicable to participants who were previously randomized to receive placebo in the double-blind study phase only.

10. **PK sampling:** Refer to Protocol Section 8.5 and central laboratory manual for sample processing details.

    10a. Serial PK: Only applicable to participants who were previously randomized to receive placebo in the double-blind study phase. PK samples should be collected on OLE Cycle 1 Day 1 at the following timepoints: pre-dose and 0.25-, 0.5-, 1-, 1.5-, 2- and 3-hours post-dose. All efforts will be made to

obtain within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing. Out of window PK draws will not be captured as deviations if the exact time of the sample collection is noted on the source documents and eCRF.

10b. Trough PK: The evening before applicable study visit, participants will record the exact time study treatment was taken in the eDiary using the home ePRO device. Participants will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.

11. **Safety labs (hematology, serum chemistry, and hormone levels):** Refer to Protocol Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. The time of hormone level blood draws should also be recorded.

    11a. At baseline, blood draws for hematology, serum chemistry, and hormone levels will be done as part of the double-blind EOT visit (prior to unblinding). However, if hematology and serum chemistry safety labs have not been conducted within the 14 days prior to C1D1, an additional blood draw will be required for same day local laboratory processing to reconfirm adequate organ and bone marrow function (refer to OLE inclusion criteria 2) and must be done prior to first dose of open-label study treatment.

12. **Urinalysis:** Refer to Protocol Section 10.2 for a complete list of analytes and the central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results and only if blood or protein is abnormal.

13. **Urine pregnancy tests:** Only required for WOCBP. Refer to Protocol Sections 8.2.6 and 10.4 for more detail.

    13a. Following Cycle 4 Day 1 study visit, all WOCBP participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to study reference manual for additional details).

14. **PROs:** Participants will complete the questionnaires using a home ePRO device (Protocol Section 8.1.2). Refer to Protocol Table 9 for the PRO administration schedule.

15. **Tumor imaging:** CT (contrast required unless contraindicated) or MRI (no contrast required) using RECIST v1.1 (modality to be determined by the investigator) is required. Whichever imaging modality is used to measure the tumor by RECIST v1.1 at screening in the double-blind phase must be used at each subsequent visit throughout the OLE phase. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review. Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.

    15a. Scan is required every 3 cycles until Cycle 13 Day 1, and then every 6 cycles thereafter.

    15b. At EOT, scan is only required if not performed within the past 3 months.

16. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles during study visits.

17. **Study treatment administration/diary:** Participants will self-administer study treatment at 150 mg (3 × 50 mg tablets) BID (approximately every 12 hours, without regard to food), continuously in 28-day cycles throughout the study. Participants should record daily administration of each study treatment dose in the eDiary using the home ePRO device. (Protocol Section 6.1).

18. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit). Refer to Protocol Section 8.2.7 for more detail.

19. **AEs/SAEs:** Will be monitored and documented from the time of informed consent and up to 30 days after the last dose of study treatment. Refer to Protocol Section 8.3 for more detail. Females reporting AEs/AESIs/SAEs of POI and/or amenorrhea will have hormone levels assessed every three months until event resolution (or for at least 90 days after discontinuing study treatment).

20. **End of treatment (EOT) visit:** Should be conducted prior to study treatment discontinuation or as close as possible to the last dose of open-label study treatment.

21. **Follow-up visit:** Only required for participants who are not transitioning directly to commercial nirogacestat (or sponsor's Continued Access Plan) at time of discontinuation. The follow-up visit will occur 30 days (+7 days) after the last dose of study treatment.

1.2.5. Efficacy and Safety Endpoints

1.2.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, which is defined as the time (in months) from randomization until the date of assessment of progression or death by any cause (whichever occurs first). Specifically,

PFS = (Date of progression or death – Date of randomization +1) / 30.4375

Progression will be determined radiographically using RECIST v1.1 (Eisenhauer, 2009) or clinically as assessed by the investigator. Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF. Events of clinical progression will be adjudicated by an independent blinded central Endpoint Adjudication Committee (EAC) which will qualify events of clinical progression for inclusion in the PFS endpoint prior to study unblinding according to an EAC Review Charter.

Study participants who discontinue the study due to clinical progression and the progression does not qualify as determined by EAC will be censored at the time of last response assessment.

Participants who have not progressed or died will be censored based on the rules outlined in Table 5. Participants who do not have any response assessments will be censored at the date of randomization. Sensitivity analysis utilizing alternative censoring methods will be described in Section 4.3.1.2.

1.2.5.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Objective Response Rate (ORR), defined in Section 4.3.2.1
    - Duration of responses (in months) as supportive, descriptive analyses of ORR, defined in Section 4.3.2.1.1
- Change in PRO measures from baseline over time, as defined in Section 4.3.2.2 (as well as in the PRO Addendum):
    - GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale
    - Brief Pain Inventory (BPI) short form
    - European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-Core 30 (QLQ-C30)

1.2.5.3. Exploratory Endpoints

Exploratory efficacy endpoints include:

- Change in tumor volume from baseline as assessed by MRI volumetric
- Changes using the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC)
- Frequency and distribution of germline and somatic mutations in APC and CTNNB1 genes
- Change in expression pre- and post-dose on Notch pathway genes
- Percent change in MRI T2 intensity
- PK samples to increase precision of model parameters
- Exposure-response analysis using a final population PK/PD (PopPK/PD) model to determine relationship between exposure and primary, secondary and/or exploratory efficacy and safety endpoints
- The incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity which may include hospitalization as a result of small bowel obstruction, hospitalization due to desmoid tumor-related pain or surgery for desmoid tumor

1.2.5.4. Safety Parameters

The safety endpoints are evaluated by means of study treatment-related AE reports, physical examinations, and laboratory safety evaluations.

AEs will be monitored continuously via safety laboratory assessments, ECGs, vital signs, and physical examinations. Clinically significant changes in physical examination findings, laboratory assessments, and vital signs will be reported as AEs.

2. SUBJECT POPULATION

2.1. Population Definitions

The following participant populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: The ITT Population will consist of all participants who are enrolled and randomized to study treatment (nirogacestat or placebo). Participants will be analyzed according to the treatment they were randomized to and the strata to which they have been assigned. Participants who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

- Per-Protocol (PP) Population: The PP Population will consist of those participants who received study drug and have no major protocol deviations. Major protocol deviations are defined in Section 2.2. and will be determined prior to unblinding. Participants will be analyzed according to the study treatment actually received. In addition to major protocol deviations, those participants who meet the following criteria may also be excluded from this population:

    - Do not have confirmed diagnosis of DT/AF per Inclusion Criterion #2

    - Mis-randomization

    - Permanent discontinuation due to non-compliance with study drug

- Safety Population: The Safety Population will consist of all participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

The ITT population is the primary analysis population for the efficacy analyses. The PP population will be used for supportive analyses as needed. The Safety population will be the primary analysis population for the safety analyses.

2.2. Protocol Deviations

Protocol deviations are reviewed in accordance with the Protocol Deviation Plan prior to unblinding of the study results and the conduct of the primary statistical analyses. A data listing of all reportable PDs including a description of the deviation will be generated. Major protocol deviations are defined as reportable deviations that may impact the accuracy and or reliability of the efficacy data. Major protocol deviations impacting the efficacy analysis will be identified prior to conducting the primary statistical analysis.

The number and percentage of participants with reportable protocol deviations not due to COVID-19 and reportable protocol deviations due to COVID-19 will be summarized overall and by category of deviation, including inclusion/exclusion criteria, investigational product, restricted concomitant medication use, study-required imaging, withdrawal criteria, safety reporting, informed consent, study procedures, and study required ePRO assessments.

2.3. Impacts from COVID-19

This study was conducted during the global SARS-Cov-2 pandemic. The impact of COVID-19 was mitigated based on the evolving EMA and FDA COVID-19 guidelines [European Medicines Agency 2021; US Food and Drug Administration 2020].

A summary table and listing of all patients impacted by COVID-19 and how their participation in the study was altered, including missed visits, missed assessments and other deviations from protocol procedures due to COVID-19 will be provided.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The study sample size is based on the primary PFS endpoint. A total of 51 events will provide 90% power and a 1-sided type 1 error rate of 0.025 (1-side hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat group is 20 months and 8 months in the placebo group (corresponding to a hazard ratio of 0.4 relative to placebo). Assuming a 10% dropout rate and a 20% spontaneous regression rate, 118 participants will be randomized in a 1:1 ratio to observe the required number of events.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day associated with double-blind phase treatment start (Rel Day). Pre-treatment and on-treatment study days in double-blind phase represented as Rel Day are numbered relative to the day of the first dose of study medication in double-blind phase which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc. If applicable, placebo subjects that have entered open-label phase will have a second relative study day derived associated with starting active treatment within open-label phase (OLE Day). On-treatment study days in open-label phase for placebo subjects represented as OLE Day are numbered relative to the day of first dose of open-label treatment which is designated as OLE Day 1 and will follow same rules as Rel Day.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of participants, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

Formal statistical hypothesis testing on the primary endpoint, for the purpose of New Drug Application (NDA), will be conducted at the 1-sided, 0.025 level of significance. Type I errors for secondary endpoints will be controlled using a hierarchical testing procedure. Summary statistics and modeling results for secondary and exploratory endpoints will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

Data will be presented by participant and summarized by treatment.

Graphical displays will be provided where useful to aid in the interpretation of results.

In addition, the following data conventions will be applied:

- P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places
- P-values less than 0.001 will be presented as "<0.001;" P-values greater than 0.999 will be presented as ">0.999"
- CIs will be presented to 1 more decimal place than the raw data
- Weeks will be calculated as number of days divided by 7
- Months will be calculated as number of days divided by 30.4375
- Years will be calculated as number of days divided by 365.25
- Cycles as used in adverse event summaries are defined as every 28 days
- Day 1 will be considered as the first day of treatment in double-blind phase
- All tables, figures, and listings will include footers at the bottom of the page reflecting the path of the programs used to generate the tables, figures, and listings, and date and time of the generation of the output

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version March 2019 or later.

3.4. Baseline Definitions

For all analyses, baseline for the double-blind phase will be defined as the most recent measurement prior to or on the first administration of study drug. For the OLE phase, baseline will be defined as the most recent assessment prior to the first administration of nirogacestat. Therefore, for participants who are assigned to the placebo arm during the DB phase and who enter the OLE phase, this will result in a secondary baseline for OLE which will be defined as the most recent measurement prior to the first administration of active treatment.

3.5. Methods of Pooling Data

Data will be pooled across study sites.

3.6. Adjustments for Covariates

The stratified log-rank test and Cox proportional hazards model will include the randomization strata as a covariate (strata). In general, the stratification factor will be included in the analysis of the primary and secondary endpoints.

Analyses accounting for baseline demographics or disease characteristics may be conducted as part of supportive analyses. This includes each of the subgroup variables listed in Section 3.8 which will be considered for inclusion as covariates in the multivariable models where noted.

3.7. Multiple Comparisons/Multiplicity

Multiplicity will be controlled via hierarchical testing method for the primary and secondary endpoints in the order as listed in Section 4.3.

3.8. Subgroups

Select efficacy endpoints (PFS and Objective Response Rate [ORR]) will be examined in (tables and forest plots) the following subgroups:

Table 3. Subgroup for Efficacy Analyses

Stratification	
Stratification factor as reported in randomization	
Demographics	
Sex (Male vs Female)	Age (by quartile)
Race (White vs Non-White)	Ethnicity
Geographic region (North America vs the rest of world)	BMI (18.5 kg/m^2, 18.5 - < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
Disease Characteristics	
Multi-focal disease vs single tumor	Baseline target lesion size by quartile
Baseline target lesion locations[1]	
Prior Treatment	
Any prior therapy (Yes vs No)	Number of prior lines of therapies (0, 1-3, 4+)
Prior systemic therapy (Yes vs No)	Prior surgical treatment (Yes vs No)
Prior radiation treatment (Yes vs No)	Previous exposure with sorafenib (Yes vs No)
Prior chemotherapy exposure (Yes vs No)	Prior tyrosine kinase inhibitor exposure (Yes vs No)
	Desmoid tumor treatment status[2]
Dose Modification	
Dosed per protocol vs reduction (Yes vs No)	Relative Dose Intensity (≤ 80% vs > 80%)
Genetic Mutation	
History of familial adenomatous polyposis (FAP)	Presence of any CTNNB1 mutation, somatic CTNNB1 mutation, or germline CTNNB1 mutation
Presence of any APC mutation, somatic APC mutation, or germline APC mutation	
Adverse Event	
Highest Reported FSH in women of childbearing potential (WOCBP) by range indicator (Low/Normal, High)	WOCBP with events of primary ovarian insufficiency (POI) that have resolved versus those that have not resolved
Participants with AEs of Rash or Alopecia	Participants with AEs of Diarrhea within the first 3 cycles

[1] Baseline target lesion location is based on actual target tumor location from the Electronic Database. Baseline target lesion locations: Intra-Abdominal (including mesentery and pelvis) and Extra-Abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations). If a participant has multiple target tumors that are located in both the intra and extra-abdominal location, the tumor will be classified as intra-abdominal.
[2] Desmoid tumor treatment status: 1) Treatment naïve, measurably progressing DT/AF, 2) Recurrent, measurably progressing DT/AF following at least one line of therapy, and 3) Refractory, measurably progressing DT/AF following at least one line of therapy

TEAE and treatment-related AEs will be examined in the following subgroups:

Table 4 Subgroup Definition for Safety Analyses

Stratification	
Stratification factor as reported in randomization	
Demographics	
Sex (Male vs Female)	Age (by quartile)
Race (White vs Non-White)	Ethnicity
Geographic Region (North America vs the rest of world)	BMI (18.5 kg/m^2, 18.5 - < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
Disease Characteristics	
Multi-focal disease vs single tumor	Baseline target lesion size by quartile
Baseline target lesion locations[1]	
Prior Treatment	
Any prior therapy (Yes vs No)	Number of prior lines of therapies (0, 1-3, vs 4+)
Prior systemic therapy (Yes vs No)	Prior surgical treatment (Yes vs No)
Prior radiation treatment (Yes vs No)	Previous exposure with sorafenib (Yes vs No)
Prior chemotherapy exposure (Yes vs No)	Prior tyrosine kinase inhibitor exposure (Yes vs No)
Desmoid tumor treatment status[2]	
Dose Modification	
Dosed per protocol vs reduction (Yes vs No)	Relative Dose Intensity (≤ 80% vs > 80%)
Genetic Mutation	
History of familial adenomatous polyposis (FAP)	Presence of any CTNNB1 mutation, somatic CTNNB1 mutation, or germline CTNNB1 mutation
Presence of any APC mutation, somatic APC mutation, or germline APC mutation	

[1] Baseline target lesion location is based on actual target tumor location from the Electronic Database. Baseline target lesion locations: Intra-Abdominal (including mesentery and pelvis) and Extra-Abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations). If a participant has multiple target tumors that are located in both the intra and extra-abdominal location, the tumor will be classified as intra-abdominal.
[2] Desmoid tumor treatment status: 1) Treatment naïve, measurably progressing DT/AF, 2) Recurrent, measurably progressing DT/AF following at least one line of therapy, and 3) Refractory, measurably progressing DT/AF following at least one line of therapy.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Participants who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR. Methods for

handling incomplete PRO instruments will be performed according to their scoring manuals, if available. The imputation of partial/missing dates for AEs, concomitant therapies/medications, and disease history/prior therapies are described in Section 7.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there is data from an unscheduled or additional visit that is inside the visit window, the data from the unscheduled or additional visit will be used in data summaries. In data listings, the relative day of all dates to first study dose will be presented.

4. STUDY ANALYSES

4.1. Disposition

The total number of participants who were screened (who have signed the informed consent), the number randomized, and the number in each study population will be summarized by treatment arm and overall. The number of randomized participants in each primary tumor location stratum will also be presented.

In addition, summaries will be presented for the number and percent of participants who:

- Discontinued treatment and reasons for treatment discontinuation in the double-blind phase
- Discontinued the study and reasons for study discontinuation
- Continued to the open label study
- Discontinued treatment and reasons for treatment discontinuation in the OLE phase
- Participants who discontinued double-blind treatment but chose to not enter OLE

All treatment and study discontinuation data will be listed. A by-participant data listing of inclusion and exclusion criteria not met will be presented.

4.2. Demographics, Baseline Characteristics, and Medical History

Demographics and baseline characteristics will be summarized for the ITT and Safety populations by treatment arm and overall. In addition, medical history (including overall medical history and any history of infertility) and disease characteristics will also be summarized for the safety and ITT populations.

Demographics will include univariate statistics for age at time of informed consent (years), baseline weight, baseline height, baseline body mass index (kg/m^2); and categorical summaries for sex, women of childbearing potential (yes / no) for females, menstrual history for females, infertility history for males and females, age, baseline ECOG, race, ethnicity, BMI group and geographic region. Menstrual history for females includes history of amenorrhea (yes / no) and menstrual irregularities (yes / no) collected on the eCRF page.

Disease characteristics to be summarized include time (in month) since date of diagnosis to randomization, presence of multi-focal disease versus single tumor, number of target tumors and target tumor location(s), desmoid tumor treatment status (treatment-naïve, recurrent or refractory disease), baseline target lesion size, family history of FAP, any mutation of APC or CTNNB1, somatic mutation status of APC and CTNNB1, germline mutation status of APC and CTNNB1 and total number of non-target tumors seen by central reviewers and location(s) of non-target tumors based on stratification factor and as reported in EDC.

Demographic and baseline data for each participant will be provided in data listings.

4.2.1. Prior Therapy

Prior therapies will be summarized by treatment arm and overall based on the ITT population. The variables will include any prior therapy (surgery, radiation, systemic) (yes / no), prior therapeutic surgery (yes / no) and resection margins, prior radiation therapy (yes / no), prior sorafenib exposure (yes / no), prior TKI exposure (yes/no) [defined as medications in the ATC classes of 'BCR-ABL TYROSINE KINASE INHIBITORS', "OTHER PROTEIN KINASE INHIBITORS'], prior systemic therapy (yes / no), type of prior systemic therapies, number of lines of prior systemic therapies and responses, and months from most recent prior systemic therapy to randomization. The total number of prior therapies will also be summarized by treatment arm and overall.

The duration to be summarized is defined as follows.

- Months from most recent prior systemic therapy to randomization will be calculated as (date of randomization – stop date of most recent systemic therapy) / (30.4375).

The imputation of partial/missing dates is described in Section 7.

Additionally, prior surgeries and systemic therapies will be presented in separate tables summarizing SOC (or ATC) and PT by treatment arm and overall. Prior radiotherapies will also be summarized by type by treatment arm and overall. Prior systemic therapies will be summarized using modified PT. PTs will be modified to be grouped as outlined in Appendix 7.4 to consolidate brand and generic medication names for the same active ingredient into a single line item to facilitate reporting of the same medication. Both the original and modified PTs will be included in the listings. If a participant experiences multiple surgeries or procedures under the same PT (or SOC/ATC), then the participant will be counted only once for that PT (or SOC/ATC).

All prior therapy data will be listed in participant data listings.

4.3. Efficacy Evaluations

The primary and secondary efficacy endpoints will be tested in the following order: PFS, objective response rate, disease symptoms, impact, and quality of life evaluations by PRO. If the null hypothesis is rejected at the specified significance level, the testing may proceed to the next endpoint, but if the null hypothesis is not rejected, all subsequent results will be considered descriptive only. All data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed and reported separately.

Efficacy analyses will be conducted using the ITT population.

4.3.1. Primary Efficacy Evaluation

The primary efficacy endpoint is PFS, where disease progression is determined by either independent, blinded central imaging review using RECIST v1.1 as described in Section 8.1.2 of the protocol, or clinically as assessed by an investigator whose assessment is qualified via

independent blinded central clinical review as described in Section 8.1.2 of the protocol. The primary efficacy analysis will be performed after approximately 51 events have been observed. PFS will be analyzed using a 1-sided stratified log-rank test to compare the distributions between nirogacestat and placebo at alpha level of 0.025. PFS data will be summarized with Kaplan-Meier methodology. Two sided 95% CIs for the median time-to-event in each study treatment arm and the hazard rate ratio will be computed.

PFS will be calculated from time of randomization to the earlier date of progression or death due to any cause. The progression date will be determined based on the date of scan for events that are verified by blinded independent central imaging review using RECIST v1.1. For qualified events of clinical progression, it will be the earliest date of onset or worsening of symptoms resulting in a global deterioration of health status.

In situations where study participants are discontinued early from the study by investigators for clinical progression but cannot be verified as qualified events, they will be considered as dropouts and will be censored for the primary analysis. Similarly, participants who do not progress or die will be censored at the date of the last valid computed tomography (CT)/MRI assessment.

Censoring rules for the primary analysis are outlined in Table 5.

Table 5 Primary PFS Censoring Methodology

Situation	Date of Censoring of Event	Outcome
No adequate disease status assessment	Date of randomization	Censored
No documented progression or death	Date of last adequate disease status assessment	Censored
Progression that has been verified by the central imaging review using RECIST v1.1 with ≤1 missing consecutive scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of progression	Event
Early discontinuation by study investigator due to clinical progression that has been verified as qualified event by the independent Event Adjudication Committee (EAC) for primary analysis	Earliest date of onset or worsening of symptoms resulting in a global deterioration of health status as documented by the date of clinical progression in the case report form	Event
Early discontinuation by study investigator due to clinical progression that do not meet the definition of a qualified event per protocol as judged by the EAC.	Date of last adequate disease status assessment	Censored
Death before progression being documented with ≤1 missing scheduled disease status assessment before death	Date of death	Event
New anticancer therapy or procedure started prior to documented radiographic or clinical progression	Date of last adequate disease status assessment before the new therapy	Censored

4.3.1.1. Analysis of Progression Free Survival

Kaplan-Meier curves will be presented, and HR and the 95% CI will be estimated using a Cox proportional hazards model controlling for stratification factor the participant is assigned to at randomization (primary tumor location - intra-abdominal vs extra-abdominal).

A stratified log-rank test on PFS will be performed using SAS PROC LIFETEST with method = PL option (Kaplan-Meier estimates, also known as the product-limit estimates). The hazard ratio with 2-sided 95% CI will be estimated from the stratified Cox proportional hazards model using SAS PHREG procedure with ties = EXACT option in the model. In this analysis, the baseline hazard function will be allowed to vary across strata, i.e., the MODEL statement will include treatment arm variable as the only covariate and the STRATA statement will include tumor location.

Number of participants with events, types of events (progression or death before progression), number of participants censored, number of participants for each reason of censoring, quartiles (i.e., the 25th, 50th (median), 75th percentile estimates), and 95% confidence intervals for PFS will be calculated from the product-limit method and presented by treatment arm. Kaplan-Meier plots of the survival distribution function will be presented and include the number of participants at risk over time by treatment arm. Additionally, a spider plot of percent change from baseline in tumor size over time will be presented. Time at which best overall response occurred (for participants with CR or PR) will be annotated as will when the participant is off treatment. A swimmer plot of duration of treatment will be produced where progression, first response, and death are noted.

4.3.1.2. Sensitivity Analyses of PFS

The following sensitivity analyses will be performed

a) Calculation of PFS using only events confirmed by central radiographic review per RECIST v1.1
b) Calculation of PFS including all PI-determined clinical progressions to assess the impact of the criteria used to determine qualified event adjudicated by EAC on the primary endpoint
c) Analysis using the PP set using the primary endpoint censoring rules
d) Using the date of the first missing assessment as the date of progression for participants who progressed radiographically right after 2 or more consecutively missed radiological assessments
e) Using local RECIST results of PI selected target tumor, instead of results from the central review, for the 15 participants whose scans are read prior to the implementation of Protocol Amendment 2 (which included the implementation of PI selection of target lesions for central review)
f) Additional sensitivity analyses using only subjects with centrally confirmed diagnosis of DT/AF

g) A sensitivity analysis using interval-censoring methodology for PFS will be performed. When the exact date of progression is not observed due to scheduled assessment, these progression events are considered interval censored. The right side of the interval will be the date of progression as defined in Table 5, and the left side of the interval will be the last adjudicated assessment for disease progression before the right side of the interval. If there is no adjudicated assessment before the date of progression, the left side of the interval will be the randomization date. Participants without a PFS qualified event will be right censored with the same censoring rules as specified in Table 5.

   A generalized stratified log-rank test stratified by the stratification factor will be performed for treatment comparison using SAS PROC ICLIFETEST (Guo, et al, 2014). This procedure will also be used to estimate the survival function for PFS with the EMICM method, which is a combination of the EM algorithm and iterative convex minorant algorithm. A multiple imputation method will be used to estimate the standard error of the survival function using SEED =138207.

In addition, to estimate the median PFS follow-up time at the time of analysis, a time-to censoring analysis will be performed by reversing the censoring indicator used in the primary PFS analysis, i.e., the censored becomes an event and the PFS event becomes censored.

4.3.1.3. Subgroup Analysis

Subgroup analyses of the primary efficacy will be performed on the ITT population using the subgroups specified in Section 3.8. If there are too few events (≤5) in a particular subgroup level, only descriptive summaries will be provided.

For each subgroup, HR and associated CIs will be calculated from a stratified Cox proportional hazards model. The stratification factor in the primary analysis will be used in the subgroup analyses when applicable. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI for the overall group. Summaries of the number and percentage of participants experiencing a PFS event for each subgroup will be provided along with the median PFS by treatment arm.

4.3.2. Secondary Efficacy Evaluations

Secondary endpoints are described in Section 1.2.5.1. Secondary efficacy analyses will be conducted using the ITT population unless otherwise specified. The hierarchy for testing secondary endpoints will follow the order of their appearance below.

4.3.2.1. Objective Response Rate (ORR)

ORR will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. Response used for the definition of ORR is defined as having a confirmed Best Overall Response (BOR) of CR or PR by RECIST v1.1 during the blinded portion of the study, where BOR is defined in Section 4.3.3.1. Summaries of ORR and the 2-sided 95% exact CI will be presented.

4.3.2.1.1. Duration of Response

Duration of Objective Response and duration of stable disease are supportive, descriptive analyses for ORR. Duration of Objective Response (DoOR) is defined as the duration in months from the time measurement criteria are met for CR or PR (whichever comes first) until the date of progression or death (whichever comes first). Duration of Stable Disease (DoSD) is defined as the duration in months from the start of treatment until the date of progression or death (whichever comes first).

Pending data availability, DoOR will be analyzed using the Kaplan-Meier method based on participants with a documented response (CR or PR) only. Estimates for the 25th percentile, 50th percentile (median), and 75th percentile for DoOR (as well as the range) will be presented by treatment arms. Similarly, DoSD will be analyzed on participants with CR, PR, or SD only. Kaplan-Meier plots for DoOR and DoSD will be provided, respectively. The censoring method will be the same as that for the primary endpoint (Section 4.3.1). Since the number of the participants available for analysis is random, no formal testing between the two treatment arms will be conducted for both DoOR and DoSD.

By-participant listings will be provided for DoOR and DoSD separately. DoOR listing will include number of completed cycles before first response, date of first response, date of progression or death if any, and DoOR. DoSD listing will include date of first study treatment, date of progression or death if any, and DoSD. Censored or event will be marked. Additionally, to evaluate efficacy compared to previous treatment, number of prior therapies will be added to the listings. Swimmer plots will be used to present duration of responses over time for each participant.

4.3.2.2. Analysis of PRO Assessment data

Due to the number of instruments used in the study and the complexity of the planned analyses, a PRO Addendum was created specifically to detail the PRO data analysis methods to be used. The endpoints and testing hierarchy for PRO data analysis can be found in this addendum and are repeated below.

Secondary efficacy endpoints related to the PRO, and their testing order, are as follows:

- Mean change from baseline at Cycle 10 in BPI-SF Average Pain Intensity (API) score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score

- Mean change from baseline at Cycle 10 in Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL)
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Physical Functioning
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Role Functioning

The PROMIS questionnaire will not be formally tested in the endpoint hiearchy.

4.3.3. Exploratory and Other Supportive Efficacy Analyses

4.3.3.1. Best Overall Response (BOR)

Confirmed BOR is defined as the best response obtained across all time points during the DB phase of the study provided after application of the following confirmation rules:

Rule 1: PR or CR require confirmation by a subsequent scan. To be allowed to confirm a PR or a CR, a time point must be at least 4 weeks after the initial PR or CR is observed.

Rule 2: To be assigned SD as a BOR, a participant is required to have at least one non-PD/non-Evaluable (NE) time point response at least 8 weeks after baseline and not meet requirements for BOR of PR or CR.

Rule 3: When one or more NE time points are interleaved between CR or PR time points, these NE time points will not impact response confirmation. As an example, a participant with PR-NE-PR will be assigned a BOR=PR (provided the second PR meets rule 1).

Table 6 BOR Determination Table

First Time Point Response	Subsequent Time Point Response	BOR
CR	CR*	CR
CR	PD	SD provided rule 2, otherwise PD
CR	NE	SD provided rule 2, otherwise NE
PR	PR* or CR*	CR if CR is confirmed; PR otherwise
PR	SD	SD
PR	PD	SD provided rule 2, otherwise PD
PR	NE	SD provided rule 2, otherwise NE

First Time Point Response	Subsequent Time Point Response	BOR
SD	SD	SD
SD	NE	SD provided rule 2, otherwise NE
SD	PD	SD provided rule 2, otherwise PD
NE	CR, PR, SD (and no subsequent response)	SD provided rule 2, otherwise NE
NE	NE	NE

Source: MICL Imaging Review Charter

Note: CR* or PR* indicates that time interval for confirmation must apply, see rule 1.

Both confirmed and unconfirmed BOR will be calculated and summarized with frequency and two-sided 95% CI by treatment arm. A comparison between the two treatment arms will be performed using Cochran-Mantel-Haenszel test stratified by randomization factor.

4.3.3.2. Disease Control Rate (DCR)

DCR (CR+PR+SD) will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. The 2-sided 95% exact CI will also be presented

4.3.3.3. Time to Tumor Progression (TTP)

TTP is defined as the time from randomization until objective tumor progression; TTP does not include deaths. TTP will be compared between the two arms. Number of participants with progression, Kaplan-Meier quartiles (i.e., the 25th, 50th (median), 75th percentile estimates), as well as descriptive statistics will be presented by treatment arm.

4.3.3.4. PFS at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period

Proportion of participants with progression free survival at month 6, month 12 and month 24 of the treatment period will be compared between the treatment arms. Survival function estimates will be presented.

4.3.3.5. DOR at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period

Proportion of participants who have experienced response who are still responders at month 6, month 12 and month 24 following the start of response will be compared between the treatment arms. Survival function estimates will be presented.

4.3.3.6. Time to Response

Time to first response and BOR will be calculated as time in months from first dose until date of either the first documented response (CR or PR) or BOR. Summary statistics will be provided by treatment arms.

4.3.3.7. Change in Tumor Volume Assessed by MRI

Percent change in tumor volume assessed by MRI will be analyzed using a repeated measures model adjusting for baseline tumor volume and randomization strata. The analysis will use mixed model with repeated measures (MMRM) and the model will include treatment, baseline volume, visit, and randomization strata as covariates. Treatment by visit interaction will be included in the model and if significant, treatment differences will be assessed by timepoint. The covariance structure will be assumed to be unstructured, although if the matrix fails to converge, alternative structures will be used in the following order until convergence is reached: Toeplitz with heterogeneity (TOEPH), autoregressive with heterogeneity (ARH[1]), Toeplitz (TOEP), and autoregressive (AR[1]). The assessment timepoints will be analyzed as categorical. The model will use a Kenward-Rogers approximation for the degrees of freedom. Adjusted mean estimates per treatment arm and 95% CIs along with an estimate of treatment difference, 95% CI, and p-value will be presented. In addition, unadjusted summary statistics for tumor volume will be presented by visit and treatment arm. The main analysis of change in tumor volume will focus solely on the largest target lesions per subject while an additional analysis will focus on lesions that have clinically progressed.

The same analysis will be repeated on the subset of participants who discontinued the study due to PI-determined clinical progression and adjudicated as qualified event for the primary analysis by the independent EAC. A listing of tumor volume for all PI-determined clinical progressions will also be provided.

Waterfall plots of the percent change from baseline in target tumor size by tumor volume as assessed by MRI will be presented by subject with each subject color-coded based on their best overall disease response.

4.3.3.8. Change in Sum of Largest Diameter of Tumor Assessed by RECIST

Observed value, change from baseline and percent change in sum of largest diameter of tumor accessed by RECIST will be summarized over scheduled visits by treatment arm and overall.

Sum of largest diameter is called as follows:

- The diameter of each lesion is assessed by two readers.
- The sum of the lesions is calculated from the tumors identified at baseline for each visit. New tumors will not be included in the sum.

- The average sum of lesions for the two readers is calculated unless the assessments were adjudicated. In cases where the assessments are adjudicated, the adjudicated (sum) record will be used.

The readings of tumor diameters accessed by RECIST will be listed in participant data listings.

Waterfall plots of the percent change from baseline in target tumor size by RECIST v1.1 will be presented by subject with each subject color-coded based on their best overall disease response. For the RECIST tumor size plot, the percent change from baseline will be computed on the averages of sum of target lesion diameters from the two readers for each subject.

4.3.3.9. Tumor Response by Exposure

The relationship between active treatment exposure (nirogacestat) and disease response (as measured by RECIST response categories) will be explored among the actively treated participants in the following manner (through modeling when appropriate):

1. Total exposure by response status will be compared. Total exposure is defined as the total number of equivalent cycles treated at per protocol dose during the treatment period. It is defined as

   Number of equivalent cycle = total dose administered / (28 * 300mg)

2. Actual and relative dose intensities (as defined in Sec 4.4.1 below) will be compared by response status

3. Correlation between exposure, as measured by total exposure and exposure intensity, and time to first response will be investigated through Cox modeling. HRs will be compared between participants with high (> median) or low (<= median) exposure.

4. Correlation between change in tumor size/volume and exposure (total and intensity) will be explored through linear regression modeling, adjusted for baseline tumor size/volume.

5. Comparison of time to response between patients who had dose reductions vs those who had not using Cox model.

4.3.3.10. Change in Tumor Volume by Tumor Response

Actual value and change from baseline in tumor volume will be summarized over scheduled visits by treatment arm and RECIST tumor response (PD, SD, and CR/PR).

4.3.3.11. Change in Symptoms by Exposure and Change in Tumor Size/Volume

Analysis has shown that the recently created GODDESS instruments for DT patients, Desmoid Tumor Symptom Scale (DTSS) and Desmoid Tumor Impact Scale (DTIS), having good psychometric properties. Therefore, the investigation of change in DT symptoms and impact as a function of active treatment exposure and change in tumor size/volume will focus on the scores of GODDESS and its subdomains, supplemented with scores from BPI and EORTC when

appropriate. Descriptions of the instruments, item definitions and domain scale construction are provided in the PRO Addendum attached to this document.

a. Change in Symptoms by Change in Tumor Size/Volume

Correlation between symptom scores of GODDESS, BPI and EORTC and percent change in tumor size (per RECIST) / tumor volume (per MRI) will be calculated.

GODDESS subscales to consider:

- DTSS Weekly Avg Mean Score
- DTSS Pain Domain Score
- DTSS Extra-abdominal Domain Score (among participants with extra-abdominal tumor)
- DTSS Intra-abdominal Domain Score (among participants with intra-abdominal tumor)
- DTIS Physical Functioning Domain Score
- DTIS Sleep Domain Score
- DTIS Emotional Domain Score

BPI Subscales to consider:

- BPI #3 (worst pain last 24 hrs)
- BPI #5 (avg pain last 24 hrs)
- BPI Pain Severity Subscale Score
- BPI Pain Interference Subscale Score

EORTC Subscales to consider:

- QLQ-C30 Physical Functioning
- QLQ-C30 Role Functioning
- QLQ-C30 Emotional Functioning
- QLQ-C30 Cognitive Functioning
- QLQ-C30 Social Functioning
- QLQ-C30 Insomnia

b. DT Symptoms and Impact by Exposure

Difference in exposure levels (total and intensity) between responders and non-responders, as defined by clinical meaningful change in GODDESS scores and subscores, will be investigated for the overall (exposure during full double-blind period versus responder at any point in double-blind period) and within the first six cycles of the study treatment period (exposure through six cycles versus early responders through 6 cycles).

Similar comparisons will be carried out between participants who do or do not experience a clinically significant change in pain, as measured by a 2-point or more reduction in BPI #3 (worst pain in past 24 hrs).

4.3.3.12. PFS by Mutation Status in APC and CTNNB1 Genes

Besides descriptive statistics (frequency and distribution) and data listings, the relationship between germline and somatic mutation status of APC and CTNNB1 and PFS will be explored through Cox modeling.

4.3.3.13. Other Prognostic Factors

Besides genetic mutations in Section 4.3.3.12, stratified Cox proportional hazards model will be used to estimate HRs according to stratification factor and additional factors described in Section 3.6 and listed under Section 3.7 using a stepwise procedure. Possible interactions among those factors will also be explored.

4.3.3.14. Change in Expression of Notch Genes

Change between pre- and post-dose gene expression values of Notch pathway will be analyzed using mixed model. Data listing by participant will be provided. If data is not available by time of the primary analysis, this analysis will be carried out as a part of analysis at the end of OLE.

4.3.3.15. Change in MRI T2 intensity

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and overall. All MRI T2 hyperintensity results will be listed in participant data listings.

4.3.3.16. Change in MRI T2 intensity by Tumor Response

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and RECIST tumor response (PD, SD, and CR/PR). Change in MRI T2 intensity by Baseline T2 Intensity Category (90%+ vs <90%)

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and baseline T2 hyperintensity (<90% and ≥ 90%).

4.3.3.17. DT Specific Comorbidity

Comparison will be made between the treatment and placebo arms on the incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity which may include hospitalization as a result of small bowel obstruction, hospitalization due to desmoid tumor-related pain, or surgery for desmoid tumor.

4.3.3.18. Local vs Central RECIST v1.1 Readings

A concordance analysis of RECIST v1.1 results by the local site investigators vs blinded central reviewers will be attempted. Cohen's kappa test will be conducted, whenever data available. If sufficient data is not available by time of the primary analysis data cut, this analysis will be carried out after last patient, last visit for the double-blind phase of the study.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population. All data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed and reported separately.

4.4.1. Study Drug Exposure and Compliance

Extent of exposure will be summarized for each treatment arm based on the Safety population.

Exposure will be summarized by treatment arm and overall, as follows:

- Duration of exposure in months (last dose date – first dose date + 1 / 30.4375) summarized as a continuous variable

  If a data cut-off date is used at the time of analysis and participants are receiving treatment, the last dose date will be the data cut-off date

- Number and percentage of participants who received treatment with a duration of at least 1 cycle, 2 cycles, 3 cycles, 6 to < 13 cycles, 13 cycles to <25 cycles and 25 cycles or longer

- Actual dose intensity (mg/day) – calculated as the cumulative dose received / duration of exposure based on dose modification data

- Relative dose intensity (%) defined as 100 x (total cumulative dose received)/ (planned cumulative dose, where planned cumulative dose is 300 mg/day multiplied by duration of exposure) and summarized as a continuous variable

- Number and percentage of participants per relative dose intensity group (< 80% vs ≥ 80%)

- Number and percentage of participants with a dose modification (dose reduction and/or dose interruption as reported on the dose modification eCRF) as well as reasons for dose modification

- Number and percentage of participants with a dose reduction (as reported on the dose modification eCRF)

- Time (in completed cycles) to the first dose reduction and first dose interruption will be summarized as continuous variables

- Number and percentage of participants with a dose interruption including the number of days interrupted (cumulative and per interruption)

- Number and percentage of participants with study drug discontinued

A by-participant listing will be presented for exposure to study drug and dosing modifications.

4.4.2. Adverse Events

All AEs will be coded using the MedDRA coding system version 24.0 or later and displayed in tables and data listings using system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent adverse events (TEAEs), where treatment-emergent is defined per protocol as any AE with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. The imputation of partial/missing dates is described in Section 7.1.

Treatment-related TEAEs are defined as a TEAE that was considered by the Investigator to be at least possibly related to the study drugs. If the 'Relationship to study drug' is missing, then it will be imputed as 'Related to study drug' in summary tables. AE severity will be classified according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

A summary of AEs by treatment arm and overall will include the number and percentage of participants who experience at least one of the following. The total number of events will also be reported.

- TEAEs
- TEAEs related to study treatment
- Serious TEAEs
- Serious TEAEs by Relatedness
- TEAEs with CTCAE grade ≥ 3
- TEAEs with CTCAE grade ≥ 3 related to study treatment
- TEAEs by maximum severity (Grade)
- TEAEs leading to early discontinuation from study
- TEAEs leading to death
- TEAEs by Cycle of Onset *
- Rash or Alopecia TEAEs+
- Primary Ovarian Insufficiency Event by resolution status (WOCBP only)+
- Diarrhea within the first 3 cycles+

***A Cycle of Onset is assigned to each TEAE based on 28-day windows starting from treatment start. TEAEs in first five cycles are displayed separately while all TEAEs occurring from Cycle 6 to Cycle 12, and Cycle 12 onward are presented together.**

+indicates these summaries will only be included in the overall summary of AEs and will not be summarized by SOC and PT

In each tabulation of TEAEs, each participant will contribute only once (i.e., the most related occurrence, or the most intense occurrence, or the first cycle of onset) to each of the subject incidence rates in the descriptive analysis, regardless of the number of episodes.

The above categories will also be presented in tables summarizing SOC and PT by treatment arm and overall. If a participant experiences multiple AEs under the same PT (or SOC), then the

participant will be counted only once for that PT (or SOC). The number of events of each type will be displayed alongside associated subject incidence percentages.

A TEAE summary by PT only and sorted by descending frequency of the active treatment arm will also be produced.

All AEs will be listed in participant data listings.

By-participant listings will also be provided for the following: AEs leading to death, serious adverse events, and AEs leading to withdrawal or discontinuation from study.

4.4.2.1. Selected Treatment Emergent Adverse Events

Additional summary tables are planned for selected adverse events.

- Ovarian dysfunction (OD) [including the preferred terms of premature menopause, ovarian failure, and amenorrhea –WOCBP only]:
    - Summary of participants and number of events of ovarian dysfunction overall, by treatment, and by age category (<35, 35-<40, 40+)
    - Summary statistics for time to onset of first OD event (days), duration of each event (days), and time from start of first OD to resolution of all OD (days) overall, by treatment and age category (<35, 35-<40, 40+)
    - Summary of OD event outcomes overall, by treatment, and by age category (<35, 35-<40, 40+). Percentages for this summary will be out of the total number of OD events
    - Summary of prior therapy including any prior therapy (systemic/radiation/surgical, yes/no), prior radiation therapy (yes/no), prior therapeutic surgery (yes/no), or prior systemic therapy (yes/no) in WOCBP with and without ovarian dysfunction. Additionally, type of prior systemic therapies, number of lines of prior systemic therapies will be summarized.
    - Relative Intensity during Double-Blind Phase in WOCBP with and without ovarian dysfunction
    - Summary of dose modifications (reduction, interruptions, withdrawal) in participants reporting events of OD overall and by treatment
    - Summary of concomitant medications initiated for the treatment of events of OD by ATC classification and PT, grade (Grade 1-2 vs 3+) overall and by treatment
    - Summary of duration of concomitant medication use for treatment of events of OD by grade (Grade 1-2 vs 3+) overall and by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.

- Diarrhea
    - Summary statistics for time to onset of first Diarrhea event (days), duration of each event (days), and time from start of first diarrhea to resolution of all diarrhea events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of diarrhea by ATC classification and PT by treatment, grade (Grade 1-2 vs 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs of diarrhea by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.
- Hypophosphatemia
    - Summary statistics for time to onset of first hypophosphatemia event (days), duration of each event (days), and time from start of first hypophosphatemia to resolution of all Hypophosphatemia events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of hypophosphatemia by ATC classification and PT, grade (Grade 1, 2, 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs of hypophosphatemia by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.
- Rash (PTs of Abscess sweat gland, Acne, Anorectal cellulitis, Carbuncle, Cellulitis staphylococcal, Dermatitis acneiform, Dry Skin, Folliculitis, Furuncle, Groin abscess, Hidradenitis, Pash syndrome, Perineal cellulitis, Pruritis, Pseudofolliculitis, Pustule, Rash, Rash erythematous, Rash papular, Rash pruritic, Rash pustular, Skin infection, Subcutaneous abscess, Sweat gland infection and High Level term of Alopecia)
    - Add summary stats for time to onset, duration of event, and time to resolution by event grade (Grade 1, 2, 3+) and overall
    - Summary statistics for time to onset of first rash event (days), duration of each event (days), and time from start of first rash to resolution of all Hypophosphatemia events (days) overall and by treatment

- Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
- Summarize concomitant medications initiated for treatment of rash by ATC classification and PT, grade (Grade 1, 2, 3+) overall and by treatment
- Summarize duration of concomitant medication use for AEs of rash by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.

4.4.2.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for this study are defined in Protocol Section 8.3.6 and include the following groups and descriptions:

- Skin Rash (clinically significant Grade 2 and Grade ≥ 3, per CTCAE v.5)
  1. Maculopapular rash
  2. Pruritic rash
  3. Erythematous rash
  4. Folliculitis
  5. Hidradenitis suppurativa
- Elevated Liver Enzymes (reported as AESI if Grade ≥ 2, per CTCAE v.5)
  1. Aspartate Aminotransferase
  2. Alanine Aminotransferase
  3. Alkaline Phosphatase
- Electrolyte Insufficiency (Grade ≥ 3, per CTCAE v.5)
  1. Hypophosphatemia
  2. Hypokalemia
  3. Hypomagnesemia
- Drug Reactions (All grades)
  1. Allergic reaction
  2. Anaphylaxis
- Reproductive System Disorders (Grade ≥ 2, per CTCAE v.5)
  1. Amenorrhea
  2. Premature menopause / Primary ovarian insufficiency

Determination of whether an event is an AESI is based on investigator reported data. The incidence of AESI's will be summarized by AESI group and PT in tables and listed separately in participant data listings.

4.4.2.3. DT Specific Comorbidity

The incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity will be summarized by treatment arm. More details are provided in Section 4.3.3.14.

4.4.3. Clinical Safety Laboratory Assessments

Central results will be the primary results to be analyzed. However, if a subject has local lab results collected during a scheduled visit and does not have central laboratory results collected for a parameter, the local results will be included for analyses. If a subject has both central and local laboratory results collected for a lab parameter during a scheduled visit, only the central results will be included for analyses. Central laboratory results from unscheduled visits will be used in the baseline and worst post-baseline derivations only. Local unscheduled visits are excluded from derivations and summarized results.

The actual value and change from baseline will be summarized for each visit for clinical laboratory parameters (hematology, chemistry, coagulation, and hormones) by treatment arm and overall.

Laboratory results will also be summarized by maximum CTCAE grade as available. For lab tests with NCI – CTCAE classification, the shift from baseline to maximum (worst) post baseline grade will be tabulated. Shift tables will summarize the count and frequency of each CTC grade to the highest CTC grade on study and where appropriate for the lab test, will include shifts to abnormal high values or abnormal low values. Laboratory tests with bi-directional grades will be presented separately for each direction (e.g., hyperglycemia and hypoglycemia). For lab tests without NCI – CTCAE classifications, the shift from baseline to each post baseline visit as well as the shift to the worst value will be summarized using the lab range indicators (normal, high, or low).

Additional shift tables will be produced for ALT, AST, alkaline phosphatase, bilirubin, phosphorus, and creatine showing shifts from below normal range, within normal range, >1 to 2 × upper limit of normal range, >2 to 3 × upper limit of normal range, >3 to 5 × upper limit of normal range and > 5 × upper limit of normal range to the worst (highest) post baseline value. Analysis related to hormone levels will be presented according to sex and by childbearing potential for female participants.

Box and whiskers plots displaying the values over time by nominal visit will be produced for each lab test. Hormone parameters will be displayed separately by sex. Additionally, WOCBP and Women who are not of childbearing potentially will be displayed separately. WOCBP will also be displayed by OD status and treatment.

All laboratory results will be listed and laboratory tests with an abnormal result will be listed separately. A subset listing will be presented for all grade 3 or higher laboratory values. A listing of participants with AST or ALT > 3X ULN that occurred within 2 days of a bilirubin value >2 ULN will be presented.

Serum pregnancy testing data will be presented for each participant in a data listing.

4.4.4. Physical Examinations and Eastern Cooperative Oncology Group Performance Status

Physical examination abnormalities reported as AEs will be summarized along with other TEAEs.

Shift tables by treatment arm and overall will summarize the count and frequency for each shift of baseline ECOG performance status grade to worst post-baseline ECOG grade. Similar tables will be provided for shifts to better grades. The ECOG performance status grades are outlined in Table 7.

All physical examination findings and ECOG performance status results will be presented in data listings.

Table 7 Eastern Cooperative Oncology Group Performance Status Grades

Grade	Description
0+	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655

4.4.5. Electrocardiogram

The actual value and change from baseline at each time point will be summarized for 12-lead ECG parameters by treatment arm and overall. The triplicated 12-Lead ECG parameters include heart rate, PR, RR, QRS, QT and QTcF intervals. The data presented represents the average values from the triplicate ECGs.

Categorical groups of QTcF will be summarized as follows:

- Maximum post-baseline QTcF
  - ≤ 450 msec
  - > 450 and ≤ 480 msec
  - > 480 and ≤ 500 msec
  - > 500 msec
- Maximum change from baseline for QTcF
  - ≤ 30 msec
  - > 30 and ≤ 60 msec
  - > 60 msec

All ECG data will be included in a by-participant data listing. Listings will be provided for participants with abnormal or outlying values for QTcF and changes in QTcF.

4.4.6. Vital Signs

The actual value and change from baseline for all parameters (except height) will be summarized at each scheduled visit by treatment arm and overall.

Vital sign measurements will be presented for each participant in a data listing.

4.4.7. Concomitant Medications and Procedures

Concomitant medications and procedures will be coded using the WHO Drug Dictionary and are defined as any medication or procedure that did not end prior to first dose or start after the 30-day follow-up period. The handling of partial/missing start dates for concomitant therapies/medications are described in Appendix 7.2. PTs will be modified to be grouped as outlined in Appendix 7.4 to consolidate brand and generic medication names for the same active ingredient into a single line item to facilitate reporting of the same medication. Both the original and modified PTs will be included in the listings. Concomitant medications will be tabulated by anatomic therapeutic class (ATC) and modified PT by treatment arm and overall. In these tabulations, each participant will contribute only once to each ATC and modified PT regardless of number of uses.

Medications will be considered prior if they stopped before the first dose of study drug. Prior medications will be tabulated separately from concomitant medications.

All medications and procedures will be included in separate data listings; an identifier will be used to show whether a medication/procedure was prior or concomitant. Both original PT and modified PT will be presented on the listing.

4.5. Pharmacokinetic and Pharmacodynamic Analyses

A separate supplementary SAP will describe the PK parameters, PopPK/PD models, and analyses. Plasma pharmacokinetic collection dates, times, and concentration results will be displayed in a data listing.

5. CHANGES TO PLANNED ANALYSES

Notable changes from the protocol-defined statistical analyses compared to this statistical analysis plan are described below:

I. An interim analysis is no longer planned

II. "Change in tumor volume from baseline as assessed by MRI volumetric" has been moved from secondary to exploratory endpoint, per FDA comment

III. "Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks" has been moved from secondary to exploratory endpoint (as described in the PRO Addendum), due to duplications to other PROs.

IV. Duration of Response and Duration of Stable disease have been removed from the hierarchical testing of secondary endpoints as they are considered supportive of ORR.

V. Proportion of participants with improvement in BPI-SF API score at Cycle 10 has been removed from the hierarchical testing of secondary endpoints.

VI. Estimates of duration of response at Months 6, 12 and 24 have been added.

6. REFERENCES

Guo C, So Y, and Johnston G. Analyzing Interval-Censored Data with the ICLIFETEST Procedure. 2014. https://support.sas.com/resources/papers/proceedings14/SAS279-2014.pdf

Eisenhaur EA, Therasse P, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45(2):228-47.

European Medicines Agency. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. 2021 April 02 (Version 4.0).

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-556.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

The ICLIFETEST Procedure:
https://documentation.sas.com/doc/en/statug/15.2/statug_iclifetest_toc.htm

US Food and Drug Administration. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020 (Updated Jan 2021).

7. APPENDICES

7.1. Handling of Missing/Partial Dates for AEs

Adverse events with incomplete onset dates will be handled as follows for the purpose of determining treatment emergence.

If the start date is partially missing, the date will be compared to the start of administration of study drug and the end date of administration+30 days.

1. If the month and day are missing:
    - If the year of the event is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
    - If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
    - If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.
2. If the day is missing:
    - If the month and year are the same as the month of treatment, the onset date will be assigned to the date of treatment.
    - If the month and year are not the same as the month/year of treatment, then the onset day will be set to the first day of the month.

If the start date is completely missing and end date is not before the first dose of study drug, then the adverse event will be considered treatment emergent.

If the participant has died and the imputed date is later than the date of death, the date of death will be used.

7.2. Handling of Missing/Partial Dates for Concomitant Therapies/Medications

Concomitant therapies/medications with start dates that are completely or partially missing will be handled as follows for the propose of determining concomitance.

1. If the start date has the month and year but the day is missing, the therapy will be considered concomitant if the month and year are:
    a. On or after the month and year of the date of the first dose of study drug
    b. On or before the month and year of the date of the last dose of study drug plus 30 days

2. If the start date has the year, but the day and month are missing, the therapy will be considered concomitant if the year is:

    a. On or after the year of the date of the first dose of study drug

    b. On or before the year of the date of the last dose of study drug plus 30 days.

3. If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is prior to the date of the first dose of study drug, then this therapy will not be considered concomitant.

4. If the start date of concomitant therapies is completely or partially missing and the stop date of concomitant therapies is on or after the date of the first dose of study drug, then the therapy will be considered concomitant.

5. If the start date and stop date of concomitant therapies are completely missing, then the therapy will be considered concomitant.

7.3. Handling of Missing Dates for Disease History and Prior Therapies

For the purpose of calculating time from diagnosis or most recent prior therapy to randomization, partial/missing dates for diagnosis and last prior therapy completion will be imputed as follows:

- If both day and month are missing and the year is prior to the year of screening, the imputed day and month will be 01 July.

- If both day and month are missing and the year is the same as the year of screening, the imputed date will be the middle point between 01 Jan of the year and the screening date. If the middle point falls between two dates, the first of the two dates will be used.

- If day is missing and the month and year are prior to the month and year of screening, the imputed date will be 15th day of the month.

- If day is missing and the month and year are the same as the month and year of screening, the imputed date will be the middle point between the first date of the month and the screening date. If the middle point falls between two dates, the first of the two dates will be used.

- No imputation will be performed if the year is missing.

7.4. Consolidated Medication Coding

Consistent with standard conventions for coding concomitant medications using WHO Drug preferred terms, the coded term for certain medications varies based on whether the reported verbatim term was a brand name or generic name. To facilitate data reporting for the same medication, the coded terms for brand and generic named medications will be consolidated in summary tables. WHO Drug preferred terms will be combined as outlined below. For all terms not listed, the original coded term will be used. Both the original and consolidated terms can be found in the datasets.

Original Term(s)	**New Term**
Morphine sulfate MS Contin	morphine sulfate
Loperamide Hydrochloride	Loperamide
Ketorolac Tromethamine	Ketorolac
Cyclobenzaprine Hydrochloride	Cyclobenzaprine
Venlafaxine Hydrochloride	Venlafaxine
Ciprofloxacin Hydrochloride	Ciprofloxacin
Levothyroxine Sodium	Levothyroxine
Prochlorperazine Edisylate Maleate	Prochlorperazine
Cetirizine hydrochloride	Cetirizine
Diphenhydramine Hydrochloride	Diphenhydramine
Valaciclovir Hydrochloride	Valacyclovir
Oxycodone Hydrochloride	Oxycodone
Pantoprazole sodium sesquihydrate	Pantoprazole
Macrogol 3350	Macrogol
Tramadol HCL	Tramadol
Metamizole Sodium	Metamazole
Imatinib mesylate	Imatinib
Sorafenib Tosilate	Sorafenib
Tegavivint	Tegatrabetan
Vinblastine Sulfate	Vinblastine
Vinorelbine tartrate	Vinorelbine

8. CLINICAL STUDY REPORT APPENDICES

8.1. Statistical Tables, Figures and Listings to be Generated

The Table of Contents for full list of tables, figures and listings can be found in a separate document (NIR-DT-301 TFL Table of Contents.pdf).

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STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)

Protocol Number:	NIR-DT-301
Protocol Version and Date:	Amendment 5: 09 February 2021 Amendment 4: 07 July 2020 (not released to sites) Amendment 3: 27 January 2020 Amendment 2: 14 October 2019 Amendment 1: 09 July 2019 Original: 03 August 2018
Name of Test Drug:	Nirogacestat
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Placebo-Controlled
Sponsor:	SpringWorks Therapeutics 100 Washington Blvd. Stamford, CT 06902 United States
Sponsor Representative:	[redacted] Sponsor Biostatistician
Analysis Plan Date:	12 May 2022
Analysis Plan Version:	Final Version 2.0

Author:

[redacted]
PharPoint Research, Inc

Date

Sponsor Signatory

[redacted]
SpringWorks Therapeutics, Inc

Date

[redacted]
SpringWorks Therapeutics, Inc

Date

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
APC	Adenomatous polyposis coli
BOR	Best Overall Response
BPI	Brief Pain Inventory
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double-blind
DOR	Duration of response
DT/AF	Desmoid Tumors/Aggressive Fibromatosis
DTIS	Desmoid Tumor Symptom Scale
DTSS	Desmoid Tumor Impact Scale
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
FAP	Familial adenomatous polyposis
FUP	Follow-up
GODDESS	GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale
HR	Hazard ratio
IRT	Interactive response technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
OD	Ovarian dysfunction
OLE	Open-label extension
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic

Abbreviation	Definition
PP	Per-Protocol
PR	Partial response
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System Physical Function
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	International System of Units
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This document is the statistical analysis plan (SAP) for NIR-DT-301, a Phase 3, randomized, double-blind, placebo-controlled study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF). It is based on Protocol Amendment 5, dated 09 February 2021. The safety and efficacy for the double-blind phase of NIR-DT-301 will be discussed in two parts:

1. The main body of the SAP (Main SAP) will detail the statistical analyses to be conducted using clinical data for the primary analysis data cut after approximately 51 events have occurred and a final double-blind phase analysis after last-participant last visit (LPLV) for the double-blind phase of the study and
2. A patient-reported outcome (PRO) Addendum for analysis of PRO data.

As with the study's Main SAP, the PRO Addendum will be finalized before the unblinding of the clinical database once the target number of events have been observed. Analysis of pharmacokinetic (PK) data from samples collected during the study will be described in a separate PK SAP that documents the integrated PK analyses (including data from early phase studies) for nirogacestat. An End of open-label extension (OLE) SAP will be developed for the OLE phase data.

The primary analysis of safety, efficacy, and tolerability is planned after approximately 51 events have occurred in the double-blind phase of the study (primary analysis data cut). A clinical study report will be developed using the primary analysis data cut. A final analysis of the double-blind phase of the study will be performed after the last participant last visit has occurred for the double-blind phase of the study; this final analysis will inform safety and nominal p-values will be presented for efficacy endpoints, but no interpretation will be made on these results. Unless otherwise specified, the analysis covered by this document will include only clinical data collected during the double-blind (DB) phase of the study. The various SAP components for study NIR-DT-301 are summarized below:

SAP Component	Focus	SAP Completion Date
Main SAP	Analysis of safety and efficacy based on clinical data collected during the DB phase of the study including the primary analysis after approximately 51 events have occurred and end of double-blind phase analysis after (LPLV)	Prior to unblinding
PRO Addendum	Analysis of PRO data based on data collected during the DB phase of the study	Prior to unblinding
PK SAP	Integrated analysis of nirogacestat PK data, including PK samples collected in NIR-DT-301	Prior to unblinding
End of OLE SAP	Analyses for long-term outcomes based on clinical and PRO data collected during the DB and OLE phases of the study	Prior to the End of the OLE phase

1.1.2. Study Objectives

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The primary objective of this study is:

- To determine the efficacy (as defined by progression-free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF

The secondary objectives of this study are:

- To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of AEs
- To determine the Objective Response Rate (complete response [CR] + partial response [PR]) of nirogacestat in participants with progressing DT/AF
    - To describe the duration of response (DOR) and duration of stable disease (DOSD) when data is available
- To evaluate desmoid tumor symptoms and impacts using the following patient-reported outcomes (PROs):
    - GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS)
    - Brief Pain Inventory (BPI) short form
    - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30

The exploratory objectives of this study are:

- To compare tumor volume changes measured by magnetic resonance imaging (MRI) in participants with progressing DT/AF
- To evaluate desmoid tumor symptoms and impacts using the following PROs:
    - Patient Global Impression of Severity (PGIS)
    - Patient Global Impression of Change (PGIC)
- To perform genotyping for germline and somatic mutation in adenomatous polyposis coli (APC) and β-catenin genes (CTNNB1)
- To assess modulation of the Notch pathway by evaluating NOTCH response genes in tumor biopsies at screening and disease progression or end of treatment (EOT)

- To assess MRI T2 hyperintensity at baseline and post-drug administration
- To inform development of a population pharmacokinetic (PK) model of nirogacestat
- To perform exposure-response analysis using a final population PK/PD (PopPK/PD) model
- To evaluate the effect of nirogacestat on clinical events related to disease specific desmoid tumor co-morbidity

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. 142 eligible participants were randomized to study treatment (nirogacestat or placebo) in a 1:1 ratio. Randomization was stratified by primary tumor location (intra-abdominal or extra-abdominal).

This study will consist of 2 phases: the double-blind phase and the optional OLE phase. Refer to the schedule of activities (SoA Table 1 and Table 2) for details on assessments and timing of study visits.

Participants will be screened up to 28 days prior to the first dose of study treatment and eligibility will be based on inclusion and exclusion criteria provided in Section 5.1 and 5.2 of the protocol. Participants will be randomized to study treatment at Cycle 1 Day 1 using interactive response technology (IRT) and will orally administer 150 mg twice daily, continuously in 28-day cycles.

Following the baseline visit (Cycle 1 Day 1), the participants will return to the clinic for study visits at Cycle 1 (Days 8, 15, 22), Cycle 2 (Day 28), Cycle 4 (Day 1), and then on Day 1 of every 3 cycles thereafter.

1.2.2. Randomization Methodology

Randomization will be stratified based on the following tumor locations:

1. Intra-abdominal (include mesentery and pelvis)

   OR

2. Extra-abdominal (including head/neck, para-spinal, extremities, abdominal wall, chest wall, and other locations).

If the participant has multiple target tumors that are located both in the intra- and extra-abdominal location, the tumor should be classified as intra-abdominal.

1.2.3. Stopping Rules and Unblinding

For the double-blind phase, the participant, investigator, and all other clinical site personnel will be blinded to the assigned treatment allocation. All sponsor personnel will also be blinded except for the sponsor's quality assurance designee(s), safety designee(s), and clinical supply material designee(s).

If central imaging review determines that a participant has radiographic progressive disease (using Response Evaluation Criteria In Solid Tumors [RECIST] v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will then return for the EOT visit which will unblind the participant and participant will have the option to enter OLE phase, if eligible. All EOT assessments and all ongoing adverse events (AEs) / serious AEs (SAEs) must (1) be assessed for causality by the investigator or qualified designee in a blinded manner and (2) recorded in the electronic case report form (eCRF) prior to the unblinding of the study treatment allocation.

Study participants who discontinue due to clinical progression will NOT be unblinded and will NOT be eligible to enroll into the optional OLE phase of the study. These participants should be discontinued from the study after completing an EOT and follow-up (FUP) visit as specified in applicable SoA table.

If a participant discontinues study treatment for any reason other than radiographic progressive disease as determined via central review, the study treatment allocation will not be unblinded.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, are provided in Table 1 (for double-blind phase) and Table 2 (for OLE phase). Please note that references to specific sections and table numbers in the schedules (and the associated table footnotes) are referring to sections and tables within the study protocol.

Table 1. Schedule of Assessments (SoA) – Double-Blind Phase

Double-Blind Phase Cycle Number	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Week 13** *Day 85* *(± 7 days)*	**Week 25 & On** *Day 169 & On* *(± 7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Informed consent[2]	X									
I/E criteria	X	X								
Demography	X									
Medical history including menstrual history for women	X									
ECOG performance status[4]	X	X				X	X	X	X	X
Physical examination[5]	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X
Weight/height[7]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[8]	X	X[8a] *(pre-& post dose)*	X[8b] *(post dose)*			X	X	X	X	X
Laboratory										
Tumor biopsy[9]	X[9a]								X[9b] *(optional)*	
Blood for serology[10]	X									
Blood for serum pregnancy test (WOCBP only)[11]	X									
Blood for PK sampling[12]		X[12a] *(serial)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*	X[12b] *(trough)*		
Blood for pharmacogenomics[13]		X *(optional)*								
Blood for genotyping[14]		X								
Blood for safety labs[15]	X	X	X	X	X	X	X	X	X	X

Double-Blind Phase **Cycle Number**	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1** **Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Week 13** *Day 85* *(± 7 days)*	**Week 25 & On** *Day 169 & On* *(± 7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Blood for female hormone levels[15]	X	X			X	X	X	X	X	X
Blood for male hormone levels[15]		X					X	X	X	X
Urinalysis[16]	X	X				X	X	X	X	X
Urine pregnancy test (WOCBP only)[17]		X			X	X	← *(monthly)[17a]* →		X	X
Patient-Reported Outcomes (PROs)[18]										
Home ePRO device training	X									
GODDESS (symptom scale)	← *(refer to Protocol Table 8)* →					← *(monthly assessment, refer to Protocol Table 8)* →				← *(refer to Protocol Table 8)* →
BPI short form										
PROMIS PF short form 10a plus 3 additional items from PROMIS item banks										
GODDESS (impact scale)										
EORTC QLQ-C30										
PGIS										
PGIC										
Imaging and RECIST										
Pre-Randomization RECIST v1.1 Calculation Worksheet[19]	X									
CT or MRI scan for tumor measurement (using RECIST v1.1)[20]	X[20a]						X[20b]	X[20b]	X[20c]	
MRI scan for tumor volume assessment[20]	X							X[20b] *(every 6 cycles)*	X[20c]	
Local RECIST v1.1 read[20]	X[20a]						X	X[20b]	X[20c]	

Double-Blind Phase **Cycle Number**	**Screening[1]**	**Cycle 1**				**Cycle 2**	**Cycle 4**	**Cycle 7 & Every 3 Cycles[26]**	**EOT[27]**	**Follow-Up[28]**
Cycle Day		**Day 1** **Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	*(up to 28 days before Day 1)*	**Week 1** *Day 1* *(up to 48 hours prior to 1st dose)*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Week 13** *Day 85* *(± 7 days)*	**Week 25 & On** *Day 169 & On* *(± 7 days)*	*See footnote 27 for visit window*	*30 days after last dose (+7 days)*
Enrollment and Study Treatment										
Randomization[21]		X								
Study treatment dispensing[22]		X					X	X		
Study treatment administration/diary[23]		←	—	—	—	—	—	→		
Study treatment accountability							X	X	X	
Ongoing Monitoring										
Monthly wellness checks[24]	←	—	—	—	—	—	—	→		
ConMed review	←	—	—	—	—	—	—	—	—	→
AE/SAE review[25]	←	—	—	—	—	—	—	—	—	→

AE = adverse event; BID = twice daily; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = end of treatment; ePRO = electronic patient-reported outcome; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; ICF = informed consent form; I/E = inclusion/exclusion; IRT = interactive response technology; MRI = magnetic resonance imaging; OLE = open-label extension; PFS = progression free survival; PGIS = patient global impression of severity; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SoA = scheduled of activities; v = version; WOCBP = women of child bearing potential..

1. **Screening visit:** Assessments may occur up to 28 days prior to first dose of study treatment with a minimum screening period of 14 days to allow for participant completion of the screening and baseline PRO assessments (refer to Protocol Table 8 for PRO administration schedule). An extension to the screening period may be permitted on a case-by-case basis following discussion between the investigator and the medical monitor/sponsor. The reason(s) for the extension must be clearly documented.

2. **Informed consent process:** Includes participant signing the ICF and must be conducted prior to any study related procedures being performed. The date the participant signs the ICF will be Day 1 of the screening period. Refer to Protocol Section 10.1.3 for more detail on the ICF process.

3. **Baseline visit:** Assessments may be performed over a 48-hour period. All baseline assessments are to be conducted prior to first dose of study treatment except for the following assessments: post-dose 12-Lead ECGs and post-dose blood draws for pharmacokinetic (serial PK) sampling.

4. **ECOG performance status:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Protocol Section 10.7 for ECOG scale.

5. **Physical examination:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Protocol Section 8.2.2 for detail regarding physical examination requirements.
6. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature (following at least 5 minutes of rest). At baseline, assessment must be done prior to first dose of study treatment. Refer to Protocol Section 8.2.4 for more detail.
7. **Height:** Required at screening only. Weight to be collected at all visits.
8. **12-lead ECGs:** Will be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. Refer to Protocol Section 8.2.3 for more detail.

    8a. At baseline, triplicate ECGs are required at two timepoints: (1) prior to the first dose of study treatment and (2) approximately 1-hour post-dose.

    8b. At Cycle 1 Day 8, triplicate ECGs are required 1-hour (±10 minutes) post-dose.
9. **Tumor (core needle) biopsy:** If tumor biopsy and MRI are performed during the same study visit, the biopsy must be done after MRI. Refer to Protocol Section 8.1.3 and central laboratory manual for sample processing details.

    9a. At screening, tumor biopsy is only required if archival tissue is not available for study procedures. Tumor biopsy will be reviewed centrally to reconfirm diagnosis, but participant enrollment is not dependent on central review.

    9b. At EOT, tumor biopsy will be optional and additional pharmacogenomic consenting is required (Protocol Section 10.1.3).
10. **Serology:** Only required at screening and to include testing for hepatitis B virus (hepatitis B surface antigen), hepatitis C virus (hepatitis C antibody [Hepatitis C virus polymerase chain reaction, if hepatitis C antibody positive]), and human immunodeficiency virus. Refer to Protocol Section 10.2 and central laboratory manual for sample processing details.
11. **Serum pregnancy test:** Only required at screening for women of childbearing potential (WOCBP). Refer to Protocol Sections 8.3.5 and 10.4, and central laboratory manual for sample processing details.
12. **PK sampling:** Refer to Protocol Section 8.5 and Protocol Table 11, and central laboratory manual for sample processing details.

    12a. Serial PK: Required on Cycle 1 Day 1 at the following timepoints: pre-dose and 0.25-, 0.5-, 1-, 1.5-, 2- and 3-hours post-dose. All efforts will be made to obtain the sample within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing. Out of window PK draws will not be captured as deviations if the exact time of the sample collection is noted on the source documents and eCRF.

    12b. Trough PK: The evening before applicable study visits, participants will record the exact time study treatment was taken in the eDiary using the home ePRO device. Participants will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.
13. **Pharmacogenomics:** Blood sample will be optional and additional pharmacogenomic consenting is required (Protocol Section 10.1.3). At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Protocol Sections 8.8 and 10.5, and central laboratory manual for sample processing details.

14. **Genotyping:** Required blood sample for all participants unless prohibited by local regulations. At baseline, blood sample must be drawn prior to first dose of study treatment. Refer to Protocol Section 8.7 and central laboratory manual for sample processing details.

15. **Safety Labs (hematology, serum chemistry, and hormone levels):** At baseline, must be done prior to first dose of study treatment. Refer to Protocol Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. The time of hormone level blood draws should also be recorded.

16. **Urinalysis:** At baseline, must be done prior to first dose of study treatment. Refer to Protocol Section 10.2 for a complete list of analytes and the central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results and only if blood or protein is abnormal.

17. **Urine pregnancy tests:** Only required for WOCBP. At baseline, urine pregnancy test must be done prior to first dose of study treatment to reconfirm eligibility. Refer to Protocol Sections 8.2.6 and 10.4 for more detail.

    17a. Following the Cycle 4 Day 1 study visit, all WOCBP participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to the study reference manual for additional details).

18. **PROs:** Participants will complete the questionnaires and record study treatment administration in the eDiary using a home ePRO device (Protocol Section 8.1.2). Refer to Protocol Table 8 for the PRO administration schedule.

19. **Pre-Randomization RECIST v1.1 Calculation Worksheet** (Protocol Section 8.1.1.1): As part of documenting that participants have satisfied inclusion criteria 2, sites are required to complete a worksheet (provided by the sponsor). The worksheet must be submitted to the sponsor's designee during the screening period as soon as the data are available to complete the worksheet. All worksheets must be received no later than 7 days prior to C1D1 to allow for review prior to randomization (refer to study reference manual for additional details).

20. **Tumor imaging:** All scans will be submitted to the central imaging core laboratory and read by Central Imaging Review throughout the study. Refer to Protocol Section 8.1.1 and imaging manuals for more detail.

    Tumor measurement using RECIST v1.1 assessment (Protocol Section 8.1.1.2): CT scans (contrast required unless contraindicated) or MRI scans (no contrast required) will be acquired to assess tumor changes. The modality (CT or MRI) for tumor assessment is to be determined by the investigator. The imaging modality used to assess the tumor at screening must be used at each subsequent visit. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review, but participant enrollment is not dependent on central review. Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.

    Tumor volumetric assessment (Protocol Section 8.1.1.3)**:** MRI scans (no contrast required) will be acquired to assess tumor volume. All scans will be submitted to the central imaging core laboratory and assessed by Central Imaging Review.

    If applicable, CT and MRI assessments may be conducted on the same day. However, MRI with no contrast must be performed prior to CT with contrast. MRI must be done prior to tumor biopsy if assessments occur on the same visit.

    20a. Screening visit scans:

- MRI and CT scans obtained during the screening visit will serve as the participant's baseline scan for the study (CT scan only required if it is the chosen modality for RECIST v1.1 tumor measurement). Scans should be submitted to central imaging core laboratory as early in the screening period as possible to confirm scan quality is acceptable for analysis prior to randomization.
- Standard of care scan(s) acquired prior to the participant signing ICF may be used as the participant's screening visit scan(s) if obtained within 28 days of the first dose of study treatment and the quality of the scans are acceptable for analysis (as determined by the central imaging core laboratory). These scans will then be collected, stored, and documented as the screening visit scan(s). No other pre-enrollment images will be collected for central reading.

20b. On study treatment scans: Starting at cycle 4, MRI or CT scans for tumor assessment (RECIST v1.1) will be obtained every 3 cycles. Starting at cycle 7, MRI for tumor volume assessment will be obtained every 6 cycles.

20c. EOT visit scans: only required if not performed within the past 3 months.

21. **Randomization:** Participants will not be randomized to study treatment using IRT until all I/E criteria (Protocol Sections 5.1 and 5.2) have been confirmed and all pre-randomization baseline study assessments have been completed.

22. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles at applicable study visits.

23. **Study treatment administration/diary:** The first dose of study treatment (3 × 50 mg tablets) will be administered orally at the site at Cycle 1 Day 1 followed by a 3-hour observation period. Participants will administer study treatment at 150 mg (3 × 50 mg tablets) twice daily (BID) (approximately every 12 hours, without regard to food) continuously in 28-day cycles throughout the study. Participants should record daily administration of each study treatment dose in the eDiary using the home ePRO device. Refer to Protocol Section 6.1 for more detail.

24. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit). Refer to Protocol Section 8.2.7 for more detail.

25. **AEs/SAEs:** Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Refer to Protocol Section 8.3 for more detail. Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).

26. **Every 3 cycles and on:** Following Cycle 7 Day 1, participants will return every 3 cycles for study visits until death, progressive disease, discontinuation of study treatment for any reason, study is stopped by the sponsor for any reason, or required number of PFS events have been observed and primary PFS analysis has been completed.

27. **EOT visit:** EOT visit should be conducted prior to study treatment discontinuation to avoid a gap in study treatment for participants entering the OLE phase. All EOT assessments must be conducted prior to unblinding (if applicable refer to Protocol Section 6.3.2.1).

    If Central Imaging Review determines that a participant has progressive disease (using RECIST v1.1) the participant will be encouraged to return to the site as soon as possible to complete the EOT visit assessments (but no later than 14 days of becoming aware of the progression).

If the participant discontinues study treatment for any reason other than progressive disease (as determined by Central Imaging Review using RECIST v1.1), they will be encouraged to return to the site as soon as possible to complete the EOT visit assessments prior to study treatment discontinuation or as close as possible to the last dose of study treatment.

28. **Follow-up visit:** Only required for participants who are not continuing into the optional OLE phase and will occur 30 days (+7 days) after the last dose of study treatment.

Table 2. Schedule of Assessments (SoA) – Open-Label Extension Phase

OLE Phase **Cycle Number**	**Cycle 1**[5] *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2**[5]	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT**[20]	**Follow-Up**[21]
Cycle Day	**Day 1 Baseline**[3]	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Informed consent[1]	X								
I/E criteria[2]	X								
ECOG performance status[6]	*Same as double-blind EOT*				X	X	X	X	X
Physical examination[7]	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
Vital signs[8]	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
Weight	*Same as double-blind EOT*	X	X	X	X	X	X	X	X
12-lead ECG[9]	X[9a] *(post dose)*	X[9b] *(post dose)*			X	X	X	X	X
Laboratory									
Blood for PK sampling[10]	X *(serial)*[10a]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]	X *(trough)*[10b]		
Blood for safety labs[11]	X[11a]	X	X	X	X	X	X	X	X
Blood for female hormone levels[11]	X[11a]			X	X	X	X	X	X

OLE Phase **Cycle Number**	**Cycle 1[5]** *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2[5]**	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Cycle Day	**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Blood for male hormone levels[11]	X[11a]					X	X	X	X
Urinalysis[12]	*Same as double-blind EOT*				X	X	X	X	X
Urine pregnancy test (WOCBP only)[13]	*Same as double-blind EOT*			X	X	*(Monthly)[13a]*		X	X
Patient-Reported Outcomes (PROs)[14]									
GODDESS (symptom scale)					*(Monthly assessment, refer to Protocol Table 9)*		*(Quarterly assessment, refer to Protocol Table 9)*		*(Refer to Protocol Table 9)*
BPI short form									
PROMIS PF short form 10a plus 3 additional items from PROMIS item banks									
GODDESS (impact scale)									
EORTC QLQ-C30									
PGIS									
PGIC									
Imaging and RECIST									
CT or MRI scan for tumor measurement (using RECIST v1.1)[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	

OLE Phase **Cycle Number**	**Cycle 1[5]** *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2[5]**	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Cycle Day	**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Local RECIST v1.1 read[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	
Enrollment and Study Treatment									
Enrollment/first dose of open-label study treatment[4]	X								
Study treatment dispensing[16]	X					X	X		
Study treatment administration/diary[17]	←	—	—	—	—	—	→		
Study treatment accountability						X	X	X	
Ongoing Monitoring									
Monthly wellness checks[18]	←	—	—	—	—	—	→		
ConMed review	←	—	—	—	—	—	—	—	→
AE/SAE review[19]									

AE = adverse event; BID = twice daily; BPI = brief pain inventory; ConMed = concomitant medication; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = end of treatment; ePRO = electronic patient-reported outcome; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; ICF = informed consent form; I/E = inclusion/exclusion; IRT = interactive response technology; MRI = magnetic resonance imaging; OLE = open-label extension; PFS = progression free survival; PGIS = patient global impression of severity; PGIC = patient global impression of change; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SoA = scheduled of activities; v = version; WOCBP = women of child bearing potential.

1. **Informed consent process:** Includes participant signing the ICF (exclusive to the OLE study phase) and must be conducted prior to administration of the first dose of open-label study treatment. Refer to Protocol Section 10.1.3 for more detail on the process.

2. **I/E criteria:** Exclusive to the OLE phase. Refer to Protocol Sections 6.7.2 and 6.7.3 for participant eligibility criteria specific to the OLE phase.
3. **Baseline visit:** The C1D1 visit of the OLE phase should be conducted on the same day as, or within 24 hours after, the double-blind EOT visit. A longer window between the double-blind EOT and OLE C1D1 visit may be allowed with prior medical monitor approval; however, repeat assessments may be required with medical monitoring guidance depending on the length of time between double-blind EOT and OLE C1D1. All double-blind EOT visit assessments, as described in the double-blind SoA (Protocol Section 1.3.1), will be conducted **prior** to unblinding the participant's study treatment and prior to administration of the first dose of open-label study treatment.
4. **Enrollment and first dose of open-label study treatment:** Participants will be enrolled in the OLE phase using the IRT only after (1) all ongoing AEs/SAEs from the double-blind phase have been assessed for causality in a blinded manner by the investigator or qualified designee, and (2) all AE/SAE causality assessments have been entered into the eCRF. All double-blind EOT visit assessments must be completed **prior** to unblinding and taking first dose of open-label study treatment.

   Participants who were randomized to receive placebo in the double-blind phase will receive their first dose of study treatment at the site followed by a 3-hour observation period.

   Participants who were randomized to nirogacestat in the double-blind phase may take their first dose of open-label study treatment at home (observation period is not required).
5. **Study visits at Cycle 1 (Day 8, 15 and 22) and Cycle 2 (Day 28):** Only applicable for participants who were previously randomized to receive placebo in the double-blind phase. If a participant was randomized to receive nirogacestat in the double-blind phase, these study visits will not be conducted, and the participant will not be required to return to the site until Cycle 4 Day 1 visit.
6. **ECOG performance status:** Refer to Protocol Section 10.7 for the ECOG scale.
7. **Physical examination:** Refer to Protocol Section 8.2.2 for more detail regarding physical examination requirements.
8. **Vital signs:** Includes blood pressure, respiratory rate, pulse rate, and body temperature (following at least 5 minutes of rest). Refer to Protocol Section 8.2.4 for more detail.
9. **12-lead ECGs:** Will be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection. Refer to Protocol Section 8.2.3 for more detail.

   9a. At baseline, triplicate ECGs are required approximately 1-hour post-dose (open-label study treatment). Applicable only to participants who were previously randomized to receive placebo in the double-blind study phase.

   9b. At Cycle 1 Day 8 visit, triplicate ECGs are required 1-hour (±10 minutes) post-dose. Applicable to participants who were previously randomized to receive placebo in the double-blind study phase only.
10. **PK sampling:** Refer to Protocol Section 8.5 and central laboratory manual for sample processing details.

    10a. Serial PK: Only applicable to participants who were previously randomized to receive placebo in the double-blind study phase. PK samples should be collected on OLE Cycle 1 Day 1 at the following timepoints: pre-dose and 0.25-, 0.5-, 1-, 1.5-, 2- and 3-hours post-dose. All efforts will be

made to obtain within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing. Out of window PK draws will not be captured as deviations if the exact time of the sample collection is noted on the source documents and eCRF.

10b. Trough PK: The evening before applicable study visit, participants will record the exact time study treatment was taken in the eDiary using the home ePRO device. Participants will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose PK blood draw.

11. **Safety labs (hematology, serum chemistry, and hormone levels):** Refer to Protocol Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. The time of hormone level blood draws should also be recorded.

    11a. At baseline, blood draws for hematology, serum chemistry, and hormone levels will be done as part of the double-blind EOT visit (prior to unblinding). However, if hematology and serum chemistry safety labs have not been conducted within the 14 days prior to C1D1, an additional blood draw will be required for same day local laboratory processing to reconfirm adequate organ and bone marrow function (refer to OLE inclusion criteria 2) and must be done prior to first dose of open-label study treatment.

12. **Urinalysis:** Refer to Protocol Section 10.2 for a complete list of analytes and the central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results and only if blood or protein is abnormal.

13. **Urine pregnancy tests:** Only required for WOCBP. Refer to Protocol Sections 8.2.6 and 10.4 for more detail.

    13a. Following Cycle 4 Day 1 study visit, all WOCBP participants will be required to return to the site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a local laboratory that has been pre-approved by the sponsor (or designee) for this assessment (refer to study reference manual for additional details).

14. **PROs:** Participants will complete the questionnaires using a home ePRO device (Protocol Section 8.1.2). Refer to Protocol Table 9 for the PRO administration schedule.

15. **Tumor imaging:** CT (contrast required unless contraindicated) or MRI (no contrast required) using RECIST v1.1 (modality to be determined by the investigator) is required. Whichever imaging modality is used to measure the tumor by RECIST v1.1 at screening in the double-blind phase must be used at each subsequent visit throughout the OLE phase. All scans will be submitted to the central imaging core laboratory and reviewed by Central Imaging Review. Tumor measurement will also be performed locally per RECIST v1.1 using the same target lesion(s) identified on the Pre-Randomization RECIST v.1.1 Calculation Worksheet.

    15a. Scan is required every 3 cycles until Cycle 13 Day 1, and then every 6 cycles thereafter.

    15b. At EOT, scan is only required if not performed within the past 3 months.

16. **Study treatment dispensing:** Participants will be dispensed study treatment using the IRT every 3 cycles during study visits.

17. **Study treatment administration/diary:** Participants will self-administer study treatment at 150 mg (3 × 50 mg tablets) BID (approximately every 12 hours, without regard to food), continuously in 28-day cycles throughout the study. Participants should record daily administration of each study treatment dose in the eDiary using the home ePRO device. (Protocol Section 6.1).

18. **Monthly wellness checks:** Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit). Refer to Protocol Section 8.2.7 for more detail.

19. **AEs/SAEs:** Will be monitored and documented from the time of informed consent and up to 30 days after the last dose of study treatment. Refer to Protocol Section 8.3 for more detail. Females reporting AEs/AESIs/SAEs of POI and/or amenorrhea will have hormone levels assessed every three months until event resolution (or for at least 90 days after discontinuing study treatment).

20. **End of treatment (EOT) visit:** Should be conducted prior to study treatment discontinuation or as close as possible to the last dose of open-label study treatment.

21. **Follow-up visit:** Only required for participants who are not transitioning directly to commercial nirogacestat (or sponsor's Continued Access Plan) at time of discontinuation. The follow-up visit will occur 30 days (+7 days) after the last dose of study treatment.

1.2.5. Efficacy and Safety Endpoints

1.2.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, which is defined as the time (in months) from randomization until the date of assessment of progression or death by any cause (whichever occurs first). Specifically,

$$\text{PFS} = (\text{Date of progression or death} - \text{Date of randomization} + 1) / 30.4375$$

Progression will be determined radiographically using RECIST v1.1 (Eisenhauer, 2009) or clinically as assessed by the investigator. Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF. Events of clinical progression will be adjudicated by an independent blinded central Endpoint Adjudication Committee (EAC) which will qualify events of clinical progression for inclusion in the PFS endpoint prior to study unblinding according to an EAC Review Charter.

Study participants who discontinue the study due to clinical progression and the progression does not qualify as determined by EAC will be censored at the time of last response assessment.

Participants who have not progressed or died will be censored based on the rules outlined in Table 5. Participants who do not have any response assessments will be censored at the date of randomization. Sensitivity analysis utilizing alternative censoring methods will be described in Section 4.3.1.2.

1.2.5.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Objective Response Rate (ORR), defined in Section 4.3.2.1
    - Duration of responses (in months) as supportive, descriptive analyses of ORR, defined in Section 4.3.2.1.1
- Change in PRO measures from baseline over time, as defined in Section 4.3.2.2 (as well as in the PRO Addendum):
    - GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale
    - Brief Pain Inventory (BPI) short form
    - European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-Core 30 (QLQ-C30)

1.2.5.3. Exploratory Endpoints

Exploratory efficacy endpoints include:

- Change in tumor volume from baseline as assessed by MRI volumetric
- Changes using the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC)
- Frequency and distribution of germline and somatic mutations in APC and CTNNB1 genes
- Change in expression pre- and post-dose on Notch pathway genes
- Percent change in MRI T2 intensity
- PK samples to increase precision of model parameters
- Exposure-response analysis using a final population PK/PD (PopPK/PD) model to determine relationship between exposure and primary, secondary and/or exploratory efficacy and safety endpoints
- The incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity which may include hospitalization as a result of small bowel obstruction, hospitalization due to desmoid tumor-related pain or surgery for desmoid tumor

1.2.5.4. Safety Parameters

The safety endpoints are evaluated by means of study treatment-related AE reports, physical examinations, and laboratory safety evaluations.

AEs will be monitored continuously via safety laboratory assessments, ECGs, vital signs, and physical examinations. Clinically significant changes in physical examination findings, laboratory assessments, and vital signs will be reported as AEs.

2. SUBJECT POPULATION

2.1. Population Definitions

The following participant populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: The ITT Population will consist of all participants who are enrolled and randomized to study treatment (nirogacestat or placebo). Participants will be analyzed according to the treatment they were randomized to and the strata to which they have been assigned. Participants who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.
- Per-Protocol (PP) Population: The PP Population will consist of those participants who received study drug and have no major protocol deviations. Major protocol deviations are defined in Section 2.2. and will be determined prior to unblinding. Participants will be analyzed according to the study treatment actually received. In addition to major protocol deviations, those participants who meet the following criteria may also be excluded from this population:
  - Do not have confirmed diagnosis of DT/AF per Inclusion Criterion #2
  - Mis-randomization
  - Permanent discontinuation due to non-compliance with study drug
- Safety Population: The Safety Population will consist of all participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

The ITT population is the primary analysis population for the efficacy analyses. The PP population will be used for supportive analyses as needed. The Safety population will be the primary analysis population for the safety analyses.

2.2. Protocol Deviations

Protocol deviations are reviewed in accordance with the Protocol Deviation Plan prior to unblinding of the study results and the conduct of the primary statistical analyses. A data listing of all reportable PDs including a description of the deviation will be generated. Major protocol deviations are defined as reportable deviations that may impact the accuracy and or reliability of the efficacy data. Major protocol deviations impacting the efficacy analysis will be identified prior to conducting the primary statistical analysis.

The number and percentage of participants with reportable protocol deviations not due to COVID-19 and reportable protocol deviations due to COVID-19 will be summarized overall and by category of deviation, including inclusion/exclusion criteria, investigational product, restricted concomitant medication use, study-required imaging, withdrawal criteria, safety reporting, informed consent, study procedures, and study required ePRO assessments.

2.3. Impacts from COVID-19

This study was conducted during the global SARS-Cov-2 pandemic. The impact of COVID-19 was mitigated based on the evolving EMA and FDA COVID-19 guidelines [European Medicines Agency 2021; US Food and Drug Administration 2020].

A summary table and listing of all patients impacted by COVID-19 and how their participation in the study was altered, including missed visits, missed assessments and other deviations from protocol procedures due to COVID-19 will be provided.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The study sample size is based on the primary PFS endpoint. A total of 51 events will provide 90% power and a 1-sided type 1 error rate of 0.025 (1-side hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat group is 20 months and 8 months in the placebo group (corresponding to a hazard ratio of 0.4 relative to placebo). Assuming a 10% dropout rate and a 20% spontaneous regression rate, 118 participants will be randomized in a 1:1 ratio to observe the required number of events.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day associated with double-blind phase treatment start (Rel Day). Pre-treatment and on-treatment study days in double-blind phase represented as Rel Day are numbered relative to the day of the first dose of study medication in double-blind phase which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc. If applicable, placebo subjects that have entered open-label phase will have a second relative study day derived associated with starting active treatment within open-label phase (OLE Day). On-treatment study days in open-label phase for placebo subjects represented as OLE Day are numbered relative to the day of first dose of open-label treatment which is designated as OLE Day 1 and will follow same rules as Rel Day.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of participants, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

Formal statistical hypothesis testing on the primary endpoint, for the purpose of New Drug Application (NDA), will be conducted at the 1-sided, 0.025 level of significance. Type I errors for secondary endpoints will be controlled using a hierarchical testing procedure. Summary statistics and modeling results for secondary and exploratory endpoints will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

Data will be presented by participant and summarized by treatment.

Graphical displays will be provided where useful to aid in the interpretation of results.

In addition, the following data conventions will be applied:

- P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places
- P-values less than 0.001 will be presented as "<0.001;" P-values greater than 0.999 will be presented as ">0.999"
- CIs will be presented to 1 more decimal place than the raw data
- Weeks will be calculated as number of days divided by 7
- Months will be calculated as number of days divided by 30.4375
- Years will be calculated as number of days divided by 365.25
- Cycles as used in adverse event summaries are defined as every 28 days
- Day 1 will be considered as the first day of treatment in double-blind phase
- All tables, figures, and listings will include footers at the bottom of the page reflecting the path of the programs used to generate the tables, figures, and listings, and date and time of the generation of the output

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version March 2019 or later.

3.4. Baseline Definitions

For all analyses, baseline for the double-blind phase will be defined as the most recent measurement prior to or on the first administration of study drug. For the OLE phase, baseline will be defined as the most recent assessment prior to the first administration of nirogacestat. Therefore, for participants who are assigned to the placebo arm during the DB phase and who enter the OLE phase, this will result in a secondary baseline for OLE which will be defined as the most recent measurement prior to the first administration of active treatment.

3.5. Methods of Pooling Data

Data will be pooled across study sites.

3.6. Adjustments for Covariates

The stratified log-rank test and Cox proportional hazards model will include the randomization strata as a covariate (strata). In general, the stratification factor will be included in the analysis of the primary and secondary endpoints.

Analyses accounting for baseline demographics or disease characteristics may be conducted as part of supportive analyses. This includes each of the subgroup variables listed in Section 3.8 which will be considered for inclusion as covariates in the multivariable models where noted.

3.7. Multiple Comparisons/Multiplicity

Multiplicity will be controlled via hierarchical testing method for the primary and secondary endpoints in the order as listed in Section 4.3.

3.8. Subgroups

Select efficacy endpoints (PFS and Objective Response Rate [ORR]) will be examined in (tables and forest plots) the following subgroups:

Table 3. Subgroup for Efficacy Analyses

Stratification	
Stratification factor as reported in randomization	
Demographics	
Sex (Male vs Female)	Age (by quartile)
Race (White vs Non-White)	Ethnicity
Geographic region (North America vs the rest of world)	BMI (18.5 kg/m^2,18.5 - < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
Disease Characteristics	
Multi-focal disease vs single tumor	Baseline target lesion size by quartile
Baseline target lesion locations[1]	
Prior Treatment	
Any prior therapy (Yes vs No)	Number of prior lines of therapies (0, 1-3, 4+)
Prior systemic therapy (Yes vs No)	Prior surgical treatment (Yes vs No)
Prior radiation treatment (Yes vs No)	Previous exposure with sorafenib (Yes vs No)
Prior chemotherapy exposure (Yes vs No)	Prior tyrosine kinase inhibitor exposure (Yes vs No)
	Desmoid tumor treatment status[2]
Dose Modification	
Dosed per protocol vs reduction (Yes vs No)	Relative Dose Intensity (≤ 80% vs > 80%)
Genetic Mutation	
History of familial adenomatous polyposis (FAP)	Presence of any CTNNB1 mutation, somatic CTNNB1 mutation, or germline CTNNB1 mutation
Presence of any APC mutation, somatic APC mutation, or germline APC mutation	
Adverse Event	
Highest Reported FSH in women of childbearing potential (WOCBP) by range indicator (Low/Normal, High)	WOCBP with events of ovarian dysfunction (as defined by a narrow list of terms per Section 7.5.1) that have resolved versus those that have not resolved
Participants with AEs of Rash or Alopecia (as defined by all narrow terms in Section 7.5.2).	Participants with AEs of Diarrhea within the first 3 cycles

[1] Baseline target lesion location is based on actual target tumor location from the Electronic Database. Baseline target lesion locations: Intra-Abdominal (including mesentery and pelvis) and Extra-Abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations). If a participant has multiple target tumors that are located in both the intra and extra-abdominal location, the tumor will be classified as intra-abdominal.
[2] Desmoid tumor treatment status: 1) Treatment naïve, measurably progressing DT/AF, 2) Recurrent, measurably progressing DT/AF following at least one line of therapy, and 3) Refractory, measurably progressing DT/AF following at least one line of therapy

TEAE and treatment-related AEs will be examined in the following subgroups:

Table 4. Subgroup Definition for Safety Analyses

Stratification	
Stratification factor as reported in randomization	
Demographics	
Sex (Male vs Female)	Age (by quartile)
Race (White vs Non-White)	Ethnicity
Geographic Region (North America vs the rest of world)	BMI (18.5 kg/m^2, 18.5 - < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
Disease Characteristics	
Multi-focal disease vs single tumor	Baseline target lesion size by quartile
Baseline target lesion locations[1]	
Prior Treatment	
Any prior therapy (Yes vs No)	Number of prior lines of therapies (0, 1-3, vs 4+)
Prior systemic therapy (Yes vs No)	Prior surgical treatment (Yes vs No)
Prior radiation treatment (Yes vs No)	Previous exposure with sorafenib (Yes vs No)
Prior chemotherapy exposure (Yes vs No)	Prior tyrosine kinase inhibitor exposure (Yes vs No)
Desmoid tumor treatment status[2]	
Dose Modification	
Dosed per protocol vs reduction (Yes vs No)	Relative Dose Intensity (≤ 80% vs > 80%)
Genetic Mutation	
History of familial adenomatous polyposis (FAP)	Presence of any CTNNB1 mutation, somatic CTNNB1 mutation, or germline CTNNB1 mutation
Presence of any APC mutation, somatic APC mutation, or germline APC mutation	

[1] Baseline target lesion location is based on actual target tumor location from the Electronic Database. Baseline target lesion locations: Intra-Abdominal (including mesentery and pelvis) and Extra-Abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations). If a participant has multiple target tumors that are located in both the intra and extra-abdominal location, the tumor will be classified as intra-abdominal.
[2] Desmoid tumor treatment status: 1) Treatment naïve, measurably progressing DT/AF, 2) Recurrent, measurably progressing DT/AF following at least one line of therapy, and 3) Refractory, measurably progressing DT/AF following at least one line of therapy.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Participants who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR. Methods for handling incomplete PRO instruments will be performed according to their scoring manuals, if

available. The imputation of partial/missing dates for AEs, concomitant therapies/medications, and disease history/prior therapies are described in Section 7.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there is data from an unscheduled or additional visit that is inside the visit window, the data from the unscheduled or additional visit will be used in data summaries. In data listings, the relative day of all dates to first study dose will be presented.

4. STUDY ANALYSES

4.1. Disposition

The total number of participants who were screened (who have signed the informed consent), the number randomized, and the number in each study population will be summarized by treatment arm and overall. The number of randomized participants in each primary tumor location stratum will also be presented.

In addition, summaries will be presented for the number and percent of participants who:

- Discontinued treatment and reasons for treatment discontinuation in the double-blind phase
- Discontinued the study and reasons for study discontinuation
- Continued to the open label study
- Discontinued treatment and reasons for treatment discontinuation in the OLE phase
- Participants who discontinued double-blind treatment but chose to not enter OLE

All treatment and study discontinuation data will be listed. A by-participant data listing of inclusion and exclusion criteria not met will be presented.

4.2. Demographics, Baseline Characteristics, and Medical History

Demographics and baseline characteristics will be summarized for the ITT and Safety populations by treatment arm and overall. In addition, medical history (including overall medical history and any history of infertility) and disease characteristics will also be summarized for the safety and ITT populations.

Demographics will include univariate statistics for age at time of informed consent (years), baseline weight, baseline height, baseline body mass index (kg/m^2); and categorical summaries for sex, women of childbearing potential (yes / no) for females, menstrual history for females, infertility history for males and females, age, baseline ECOG, race, ethnicity, BMI group and geographic region. Menstrual history for females includes history of amenorrhea (yes / no) and menstrual irregularities (yes / no) collected on the eCRF page.

Disease characteristics to be summarized include time (in month) since date of diagnosis to randomization, presence of multi-focal disease versus single tumor, number of target tumors and target tumor location(s), desmoid tumor treatment status (treatment-naïve, recurrent or refractory disease), baseline target lesion size, family history of FAP, any mutation of APC or CTNNB1, somatic mutation status of APC and CTNNB1, germline mutation status of APC and CTNNB1 and total number of non-target tumors seen by central reviewers and location(s) of non-target tumors based on stratification factor and as reported in EDC.

Demographic and baseline data for each participant will be provided in data listings.

4.2.1. Prior Therapy

Prior therapies will be summarized by treatment arm and overall based on the ITT population. The variables will include any prior therapy (surgery, radiation, systemic) (yes / no), prior therapeutic surgery (yes / no) and resection margins, prior radiation therapy (yes / no), prior sorafenib exposure (yes / no), prior TKI exposure (yes/no) [defined as medications in the ATC classes of 'BCR-ABL TYROSINE KINASE INHIBITORS', "OTHER PROTEIN KINASE INHIBITORS'], prior systemic therapy (yes / no), type of prior systemic therapies, number of lines of prior systemic therapies and responses, and months from most recent prior systemic therapy to randomization. The total number of prior therapies will also be summarized by treatment arm and overall.

The duration to be summarized is defined as follows.

- Months from most recent prior systemic therapy to randomization will be calculated as (date of randomization – stop date of most recent systemic therapy) / (30.4375).

The imputation of partial/missing dates is described in Section 7.

Additionally, prior surgeries and systemic therapies will be presented in separate tables summarizing SOC (or ATC) and PT by treatment arm and overall. Prior radiotherapies will also be summarized by type by treatment arm and overall. Prior systemic therapies will be summarized using modified PT. PTs will be modified to be grouped as outlined in Appendix 7.4 to consolidate brand and generic medication names for the same active ingredient into a single line item to facilitate reporting of the same medication. Both the original and modified PTs will be included in the listings. If a participant experiences multiple surgeries or procedures under the same PT (or SOC/ATC), then the participant will be counted only once for that PT (or SOC/ATC).

All prior therapy data will be listed in participant data listings.

4.3. Efficacy Evaluations

The primary and secondary efficacy endpoints will be tested in the following order: PFS, objective response rate, disease symptoms, impact, and quality of life evaluations by PRO. If the null hypothesis is rejected at the specified significance level, the testing may proceed to the next endpoint, but if the null hypothesis is not rejected, all subsequent results will be considered descriptive only. All data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed and reported separately.

Efficacy analyses will be conducted using the ITT population.

4.3.1. Primary Efficacy Evaluation

The primary efficacy endpoint is PFS, where disease progression is determined by either independent, blinded central imaging review using RECIST v1.1 as described in Section 8.1.2 of the protocol, or clinically as assessed by an investigator whose assessment is qualified via independent blinded central clinical review as described in Section 8.1.2 of the protocol. The primary efficacy analysis will be performed after approximately 51 events have been observed.

PFS will be analyzed using a 1-sided stratified log-rank test to compare the distributions between nirogacestat and placebo at alpha level of 0.025. PFS data will be summarized with Kaplan-Meier methodology. Two sided 95% CIs for the median time-to-event in each study treatment arm and the hazard rate ratio will be computed.

PFS will be calculated from time of randomization to the earlier date of progression or death due to any cause. The progression date will be determined based on the date of scan for events that are verified by blinded independent central imaging review using RECIST v1.1. For qualified events of clinical progression, it will be the earliest date of onset or worsening of symptoms resulting in a global deterioration of health status.

In situations where study participants are discontinued early from the study by investigators for clinical progression but cannot be verified as qualified events, they will be considered as dropouts and will be censored for the primary analysis. Similarly, participants who do not progress or die will be censored at the date of the last valid computed tomography (CT)/MRI assessment.

Censoring rules for the primary analysis are outlined in Table 5.

Table 5. Primary PFS Censoring Methodology

Situation	Date of Censoring of Event	Outcome
No adequate disease status assessment	Date of randomization	Censored
No documented progression or death	Date of last adequate disease status assessment	Censored
Progression that has been verified by the central imaging review using RECIST v1.1 with ≤1 missing consecutive scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of progression	Event
Early discontinuation by study investigator due to clinical progression that has been verified as qualified event by the independent Event Adjudication Committee (EAC) for primary analysis	Earliest date of onset or worsening of symptoms resulting in a global deterioration of health status as documented by the date of clinical progression in the case report form	Event
Early discontinuation by study investigator due to clinical progression that do not meet the definition of a qualified event per protocol as judged by the EAC.	Date of last adequate disease status assessment	Censored
Death before progression being documented with ≤1 missing scheduled disease status assessment before death	Date of death	Event
New anticancer therapy or procedure started prior to documented radiographic or clinical progression	Date of last adequate disease status assessment before the new therapy	Censored

4.3.1.1. Analysis of Progression Free Survival

Kaplan-Meier curves will be presented, and HR and the 95% CI will be estimated using a Cox proportional hazards model controlling for stratification factor the participant is assigned to at randomization (primary tumor location - intra-abdominal vs extra-abdominal).

A stratified log-rank test on PFS will be performed using SAS PROC LIFETEST with method = PL option (Kaplan-Meier estimates, also known as the product-limit estimates). The hazard ratio with 2-sided 95% CI will be estimated from the stratified Cox proportional hazards model using SAS PHREG procedure with ties = EXACT option in the model. In this analysis, the baseline hazard function will be allowed to vary across strata, i.e., the MODEL statement will include treatment arm variable as the only covariate and the STRATA statement will include tumor location.

Number of participants with events, types of events (progression or death before progression), number of participants censored, number of participants for each reason of censoring, quartiles (i.e., the 25th, 50th (median), 75th percentile estimates), and 95% confidence intervals for PFS will be calculated from the product-limit method and presented by treatment arm. Kaplan-Meier plots of the survival distribution function will be presented and include the number of participants at risk over time by treatment arm. Additionally, a spider plot of percent change from baseline in tumor size over time will be presented. Time at which best overall response occurred (for participants with CR or PR) will be annotated as will when the participant is off treatment. A swimmer plot of duration of treatment will be produced where progression, first response, and death are noted.

4.3.1.2. Sensitivity Analyses of PFS

The following sensitivity analyses will be performed

a) Calculation of PFS using only events confirmed by central radiographic review per RECIST v1.1
b) Calculation of PFS including all PI-determined clinical progressions to assess the impact of the criteria used to determine qualified event adjudicated by EAC on the primary endpoint
c) Analysis using the PP set using the primary endpoint censoring rules
d) Using the date of the first missing assessment as the date of progression for participants who progressed radiographically right after 2 or more consecutively missed radiological assessments
e) Using local RECIST results of PI selected target tumor, instead of results from the central review, for the 15 participants whose scans are read prior to the implementation of Protocol Amendment 2 (which included the implementation of PI selection of target lesions for central review)
f) Additional sensitivity analyses using only subjects with centrally confirmed diagnosis of DT/AF

g) A sensitivity analysis using interval-censoring methodology for PFS will be performed. When the exact date of progression is not observed due to scheduled assessment, these progression events are considered interval censored. The right side of the interval will be the date of progression as defined in Table 5, and the left side of the interval will be the last adjudicated assessment for disease progression before the right side of the interval. If there is no adjudicated assessment before the date of progression, the left side of the interval will be the randomization date. Participants without a PFS qualified event will be right censored with the same censoring rules as specified in Table 5.

   A generalized stratified log-rank test stratified by the stratification factor will be performed for treatment comparison using SAS PROC ICLIFETEST (Guo, et al, 2014). This procedure will also be used to estimate the survival function for PFS with the EMICM method, which is a combination of the EM algorithm and iterative convex minorant algorithm. A multiple imputation method will be used to estimate the standard error of the survival function using SEED =138207.

In addition, to estimate the median PFS follow-up time at the time of analysis, a time-to censoring analysis will be performed by reversing the censoring indicator used in the primary PFS analysis, i.e., the censored becomes an event and the PFS event becomes censored.

4.3.1.3. Subgroup Analysis

Subgroup analyses of the primary efficacy will be performed on the ITT population using the subgroups specified in Section 3.8. If there are too few events (≤5) in a particular subgroup level, only descriptive summaries will be provided.

For each subgroup, HR and associated CIs will be calculated from a stratified Cox proportional hazards model. The stratification factor in the primary analysis will be used in the subgroup analyses when applicable. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI for the overall group. Summaries of the number and percentage of participants experiencing a PFS event for each subgroup will be provided along with the median PFS by treatment arm.

4.3.2. Secondary Efficacy Evaluations

Secondary endpoints are described in Section 1.2.5.1. Secondary efficacy analyses will be conducted using the ITT population unless otherwise specified. The hierarchy for testing secondary endpoints will follow the order of their appearance below.

4.3.2.1. Objective Response Rate (ORR)

ORR will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. Response used for the definition of ORR is defined as having a confirmed Best Overall Response (BOR) of CR or PR by RECIST v1.1 during the blinded portion of the study, where BOR is defined in Section 4.3.3.1. Summaries of ORR and the 2-sided 95% exact CI will be presented.

4.3.2.1.1. Duration of Response

Duration of Objective Response and duration of stable disease are supportive, descriptive analyses for ORR. Duration of Objective Response (DoOR) is defined as the duration in months from the time measurement criteria are met for CR or PR (whichever comes first) until the date of progression or death (whichever comes first). Duration of Stable Disease (DoSD) is defined as the duration in months from the start of treatment until the date of progression or death (whichever comes first).

Pending data availability, DoOR will be analyzed using the Kaplan-Meier method based on participants with a documented response (CR or PR) only. Estimates for the 25th percentile, 50th percentile (median), and 75th percentile for DoOR (as well as the range) will be presented by treatment arms. Similarly, DoSD will be analyzed on participants with CR, PR, or SD only. Kaplan-Meier plots for DoOR and DoSD will be provided, respectively. The censoring method will be the same as that for the primary endpoint (Section 4.3.1). Since the number of the participants available for analysis is random, no formal testing between the two treatment arms will be conducted for both DoOR and DoSD.

By-participant listings will be provided for DoOR and DoSD separately. DoOR listing will include number of completed cycles before first response, date of first response, date of progression or death if any, and DoOR. DoSD listing will include date of first study treatment, date of progression or death if any, and DoSD. Censored or event will be marked. Additionally, to evaluate efficacy compared to previous treatment, number of prior therapies will be added to the listings. Swimmer plots will be used to present duration of responses over time for each participant.

4.3.2.2. Analysis of PRO Assessment data

Due to the number of instruments used in the study and the complexity of the planned analyses, a PRO Addendum was created specifically to detail the PRO data analysis methods to be used. The endpoints and testing hierarchy for PRO data analysis can be found in this addendum and are repeated below.

Secondary efficacy endpoints related to the PRO, and their testing order, are as follows:

- Mean change from baseline at Cycle 10 in BPI-SF Average Pain Intensity (API) score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL)
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Physical Functioning
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Role Functioning

The PROMIS questionnaire will not be formally tested in the endpoint hiearchy.

4.3.3. Exploratory and Other Supportive Efficacy Analyses

4.3.3.1. Best Overall Response (BOR)

Confirmed BOR (as reported from Central Imaging review) is defined as the best response obtained across all time points during the DB phase of the study provided after application of the following confirmation rules:

Rule 1: PR or CR require confirmation by a subsequent scan. To be allowed to confirm a PR or a CR, a time point must be at least 4 weeks after the initial PR or CR is observed.

Rule 2: To be assigned SD as a BOR, a participant is required to have at least one non-PD/non-Evaluable (NE) time point response at least 8 weeks after baseline and not meet requirements for BOR of PR or CR.

Rule 3: When one or more NE time points are interleaved between CR or PR time points, these NE time points will not impact response confirmation. As an example, a participant with PR-NE-PR will be assigned a BOR=PR (provided the second PR meets rule 1).

Table 6. BOR Determination Table

First Time Point Response	Subsequent Time Point Response	BOR
CR	CR*	CR
CR	PD	SD provided rule 2, otherwise PD
CR	NE	SD provided rule 2, otherwise NE
PR	PR* or CR*	CR if CR is confirmed; PR otherwise
PR	SD	SD
PR	PD	SD provided rule 2, otherwise PD
PR	NE	SD provided rule 2, otherwise NE
SD	SD	SD
SD	NE	SD provided rule 2, otherwise NE
SD	PD	SD provided rule 2, otherwise PD
NE	CR, PR, SD (and no subsequent response)	SD provided rule 2, otherwise NE
NE	NE	NE

Source: MICL Imaging Review Charter
Note: CR* or PR* indicates that time interval for confirmation must apply, see rule 1.

Confirmed BOR (as reported by central imaging review) will be summarized with frequency and two-sided 95% CI by treatment arm. A comparison between the two treatment arms will be performed using Cochran-Mantel-Haenszel test stratified by randomization factor.

4.3.3.2. Disease Control Rate (DCR)

DCR (CR+PR+SD) will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. The 2-sided 95% exact CI will also be presented

4.3.3.3. Time to Tumor Progression (TTP)

TTP is defined as the time from randomization until objective tumor progression; TTP does not include deaths. TTP will be compared between the two arms. Number of participants with progression, Kaplan-Meier quartiles (i.e., the 25th, 50th (median), 75th percentile estimates), as well as descriptive statistics will be presented by treatment arm.

4.3.3.4. PFS at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period

Proportion of participants with progression free survival at month 6, month 12 and month 24 of the treatment period will be compared between the treatment arms. Survival function estimates will be presented.

4.3.3.5. DOR at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period

Proportion of participants who have experienced response who are still responders at month 6, month 12 and month 24 following the start of response will be compared between the treatment arms. Survival function estimates will be presented.

4.3.3.6. Time to Response

Time to first response and BOR will be calculated as time in months from first dose until date of either the first documented response (CR or PR) or BOR. Summary statistics will be provided by treatment arms.

4.3.3.7. Change in Tumor Volume Assessed by MRI

Percent change in tumor volume assessed by MRI will be analyzed using a repeated measures model adjusting for baseline tumor volume and randomization strata. The analysis will use mixed model with repeated measures (MMRM) and the model will include treatment, baseline volume, visit, and randomization strata as covariates. Treatment by visit interaction will be included in the model and if significant, treatment differences will be assessed by timepoint. The covariance structure will be assumed to be unstructured, although if the matrix fails to converge, alternative structures will be used in the following order until convergence is reached: Toeplitz with heterogeneity (TOEPH), autoregressive with heterogeneity (ARH[1]), Toeplitz (TOEP), and autoregressive (AR[1]). The assessment timepoints will be analyzed as categorical. The model will use a Kenward-Rogers approximation for the degrees of freedom. Adjusted mean estimates per treatment arm and 95% CIs along with an estimate of treatment difference, 95% CI, and p-value will be presented. In addition, unadjusted summary statistics for tumor volume will be presented by visit and treatment arm. The main analysis of change in tumor volume will focus solely on the largest target lesions per subject while an additional analysis will focus on lesions that have clinically progressed.

The same analysis will be repeated on the subset of participants who discontinued the study due to PI-determined clinical progression and adjudicated as qualified event for the primary analysis by the independent EAC. A listing of tumor volume for all PI-determined clinical progressions will also be provided.

Waterfall plots of the percent change from baseline in target tumor size by tumor volume as assessed by MRI will be presented by subject with each subject color-coded based on their best overall disease response.

4.3.3.8. Change in Sum of Largest Diameter of Tumor Assessed by RECIST

Observed value, change from baseline and percent change in sum of largest diameter of tumor accessed by RECIST will be summarized over scheduled visits by treatment arm and overall.

Sum of largest diameter is called as follows:

- The diameter of each lesion is assessed by two readers.
- The sum of the lesions is calculated from the tumors identified at baseline for each visit. New tumors will not be included in the sum.
- The average sum of lesions for the two readers is calculated unless the assessments were adjudicated. In cases where the assessments are adjudicated, the adjudicated (sum) record will be used.

The readings of tumor diameters accessed by RECIST will be listed in participant data listings.

Waterfall plots of the percent change from baseline in target tumor size by RECIST v1.1 will be presented by subject with each subject color-coded based on their best overall disease response. For the RECIST tumor size plot, the percent change from baseline will be computed on the averages of sum of target lesion diameters from the two readers for each subject.

4.3.3.9. Tumor Response by Exposure

The relationship between active treatment exposure (nirogacestat) and disease response (as measured by RECIST response categories) will be explored among the actively treated participants in the following manner (through modeling when appropriate):

1. Total exposure by response status will be compared. Total exposure is defined as the total number of equivalent cycles treated at per protocol dose during the treatment period. It is defined as

   Number of equivalent cycle = total dose administered / (28 * 300mg)

2. Actual and relative dose intensities (as defined in Sec 4.4.1 below) will be compared by response status
3. Correlation between exposure, as measured by total exposure and exposure intensity, and time to first response will be investigated through Cox modeling. HRs will be compared between participants with high (> median) or low (<= median) exposure.

4. Correlation between change in tumor size/volume and exposure (total and intensity) will be explored through linear regression modeling, adjusted for baseline tumor size/volume.
5. Comparison of time to response between patients who had dose reductions vs those who had not using Cox model.

4.3.3.10. Change in Tumor Volume by Tumor Response

Actual value and change from baseline in tumor volume will be summarized over scheduled visits by treatment arm and RECIST tumor response (PD, SD, and CR/PR).

4.3.3.11. Change in Symptoms by Exposure and Change in Tumor Size/Volume

Analysis has shown that the recently created GODDESS instruments for DT patients, Desmoid Tumor Symptom Scale (DTSS) and Desmoid Tumor Impact Scale (DTIS), having good psychometric properties. Therefore, the investigation of change in DT symptoms and impact as a function of active treatment exposure and change in tumor size/volume will focus on the scores of GODDESS and its subdomains, supplemented with scores from BPI and EORTC when appropriate. Descriptions of the instruments, item definitions and domain scale construction are provided in the PRO Addendum attached to this document.

a. Change in Symptoms by Change in Tumor Size/Volume

Correlation between symptom scores of GODDESS, BPI and EORTC and percent change in tumor size (per RECIST) / tumor volume (per MRI) will be calculated.

GODDESS subscales to consider:

DTSS Weekly Avg Mean Score	DTIS Physical Functioning Domain Score
DTSS Pain Domain Score	DTIS Sleep Domain Score
DTSS Extra-abdominal Domain Score (among participants with extra-abdominal tumor)	DTIS Emotional Domain Score
DTSS Intra-abdominal Domain Score (among participants with intra-abdominal tumor)	

BPI Subscales to consider:

BPI #3 (worst pain last 24 hrs)	BPI Pain Severity Subscale Score
BPI #5 (avg pain last 24 hrs)	BPI Pain Interference Subscale Score

EORTC Subscales to consider:

QLQ-C30 Physical Functioning	QLQ-C30 Cognitive Functioning
QLQ-C30 Role Functioning	QLQ-C30 Social Functioning
QLQ-C30 Emotional Functioning	QLQ-C30 Insomnia

b. DT Symptoms and Impact by Exposure

Difference in exposure levels (total and intensity) between responders and non-responders, as defined by clinical meaningful change in GODDESS scores and subscores, will be investigated for the overall (exposure during full double-blind period versus responder at any point in double-blind period) and within the first six cycles of the study treatment period (exposure through six cycles versus early responders through 6 cycles).

Similar comparisons will be carried out between participants who do or do not experience a clinically significant change in pain, as measured by a 2-point or more reduction in BPI #3 (worst pain in past 24 hrs).

4.3.3.12. PFS by Mutation Status in APC and CTNNB1 Genes

Besides descriptive statistics (frequency and distribution) and data listings, the relationship between germline and somatic mutation status of APC and CTNNB1 and PFS will be explored through Cox modeling.

4.3.3.13. Other Prognostic Factors

Besides genetic mutations in Section 4.3.3.12, stratified Cox proportional hazards model will be used to estimate HRs according to stratification factor and additional factors described in Section 3.6 and listed under Section 3.7 using a stepwise procedure. Possible interactions among those factors will also be explored.

4.3.3.14. Change in Expression of Notch Genes

Change between pre- and post-dose gene expression values of Notch pathway will be analyzed using mixed model. Data listing by participant will be provided. If data is not available by time of the primary analysis, this analysis will be carried out as a part of analysis at the end of OLE.

4.3.3.15. Change in MRI T2 intensity

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and overall. All MRI T2 hyperintensity results will be listed in participant data listings.

4.3.3.16. Change in MRI T2 intensity by Tumor Response

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and RECIST tumor response (PD, SD, and CR/PR). Change in MRI T2 intensity by Baseline T2 Intensity Category (90%+ vs <90%)

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and baseline T2 hyperintensity (<90% and ≥ 90%).

4.3.3.17. DT Specific Comorbidity

Comparison will be made between the treatment and placebo arms on the incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity which may include hospitalization as a result of small bowel obstruction, hospitalization due to desmoid

tumor-related pain, or surgery for desmoid tumor. The list of terms included in this analysis will be identified prior to unblinding for the primary analysis.

4.3.3.18. Local vs Central RECIST v1.1 Readings

A concordance analysis of RECIST v1.1 results by the local site investigators vs blinded central reviewers will be attempted. Cohen's kappa test will be conducted, whenever data available. If sufficient data is not available by time of the primary analysis data cut, this analysis will be carried out after last patient, last visit for the double-blind phase of the study.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population. All data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed and reported separately.

4.4.1. Study Drug Exposure and Compliance

Extent of exposure will be summarized for each treatment arm based on the Safety population.

Exposure will be summarized by treatment arm and overall, as follows:

- Duration of exposure in months (last dose date – first dose date + 1 / 30.4375) summarized as a continuous variable

  If a data cut-off date is used at the time of analysis and participants are receiving treatment, the last dose date will be the data cut-off date
- Number and percentage of participants who received treatment with a duration of at least 1 cycle, 2 cycles, 3 cycles, 6 to < 13 cycles, 13 cycles to <25 cycles and 25 cycles or longer
- Actual dose intensity (mg/day) – calculated as the cumulative dose received / duration of exposure based on dose modification data
- Relative dose intensity (%) defined as 100 x (total cumulative dose received)/ (planned cumulative dose, where planned cumulative dose is 300 mg/day multiplied by duration of exposure) and summarized as a continuous variable
- Number and percentage of participants per relative dose intensity group (< 80% vs ≥ 80%)
- Number and percentage of participants with a dose modification (dose reduction and/or dose interruption as reported on the dose modification eCRF) as well as reasons for dose modification
- Number and percentage of participants with a dose reduction (as reported on the dose modification eCRF)
- Time (in completed cycles) to the first dose reduction and first dose interruption will be summarized as continuous variables
- Number and percentage of participants with a dose interruption including the number of days interrupted (cumulative and per interruption)
- Number and percentage of participants with study drug discontinued

A by-participant listing will be presented for exposure to study drug and dosing modifications.

4.4.2. Adverse Events

All AEs will be coded using the MedDRA coding system version 24.0 or later and displayed in tables and data listings using system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent adverse events (TEAEs), where treatment-emergent is defined per protocol as any AE with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. The imputation of partial/missing dates is described in Section 7.1.

Treatment-related TEAEs are defined as a TEAE that was considered by the Investigator to be at least possibly related to the study drugs. If the 'Relationship to study drug' is missing, then it will be imputed as 'Related to study drug' in summary tables. AE severity will be classified according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

A summary of AEs by treatment arm and overall will include the number and percentage of participants who experience at least one of the following. The total number of events will also be reported.

- TEAEs
- TEAEs related to study treatment
- Serious TEAEs
- Serious TEAEs by Relatedness
- TEAEs with CTCAE grade ≥ 3
- TEAEs with CTCAE grade ≥ 3 related to study treatment
- TEAEs by maximum severity (Grade)
- TEAEs leading to early discontinuation from study
- TEAEs leading to death
- TEAEs by Cycle of Onset *
- Rash or Alopecia TEAEs+
- Ovarian Dysfunction Events (as defined by a narrow list of terms per Section 7.5.1) by resolution status (WOCBP only)+
- Diarrhea within the first 3 cycles+

***A Cycle of Onset is assigned to each TEAE based on 28-day windows starting from treatment start. TEAEs in first five cycles are displayed separately while all TEAEs occurring from Cycle 6 to Cycle 12, and Cycle 12 onward are presented together.**

+indicates these summaries will only be included in the overall summary of AEs and will not be summarized by SOC and PT

In each tabulation of TEAEs, each participant will contribute only once (i.e., the most related occurrence, or the most intense occurrence, or the first cycle of onset) to each of the subject incidence rates in the descriptive analysis, regardless of the number of episodes.

The above categories will also be presented in tables summarizing SOC and PT by treatment arm and overall. If a participant experiences multiple AEs under the same PT (or SOC), then the participant will be counted only once for that PT (or SOC). The number of events of each type will be displayed alongside associated subject incidence percentages.

A TEAE summary by PT only and sorted by descending frequency of the active treatment arm will also be produced.

All AEs will be listed in participant data listings.

By-participant listings will also be provided for the following: AEs leading to death, serious adverse events, and AEs leading to withdrawal or discontinuation from study.

4.4.2.1. Selected Treatment Emergent Adverse Events

Additional summary tables are planned for selected adverse events.

- Ovarian dysfunction (OD) [separately for Narrow terms and both Broad and Narrow identified per Section 7.5. –WOCBP only]:
    - Summary of participants and number of events of ovarian dysfunction overall, by treatment, and by age category (<35, 35-<40, 40+)
    - Summary statistics for time to onset of first OD event (days), duration of each event (days), and time from start of first OD to resolution of all OD (days) overall, by treatment and age category (<35, 35-<40, 40+)
    - Summary of OD event outcomes overall, by treatment, and by age category (<35, 35-<40, 40+). Percentages for this summary will be out of the total number of OD events
    - Summary of prior therapy including any prior therapy (systemic/radiation/surgical, yes/no), prior radiation therapy (yes/no), prior therapeutic surgery (yes/no), or prior systemic therapy (yes/no) in WOCBP with and without ovarian dysfunction. Additionally, type of prior systemic therapies, number of lines of prior systemic therapies will be summarized.
    - Relative Intensity during Double-Blind Phase in WOCBP with and without ovarian dysfunction
    - Summary of dose modifications (reduction, interruptions, withdrawal) in participants reporting events of OD overall and by treatment
    - Summary of concomitant medications initiated for the treatment of events of OD by ATC classification and PT, grade (Grade 1-2 vs 3+) overall and by treatment
    - Summary of duration of concomitant medication use for treatment of events of OD by grade (Grade 1-2 vs 3+) overall and by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.

- Diarrhea
    - Summary statistics for time to onset of first Diarrhea event (days), duration of each event (days), and time from start of first diarrhea to resolution of all diarrhea events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of diarrhea by ATC classification and PT by treatment, grade (Grade 1-2 vs 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs of diarrhea by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.
- Hypophosphatemia
    - Summary statistics for time to onset of first hypophosphatemia event (days), duration of each event (days), and time from start of first hypophosphatemia to resolution of all Hypophosphatemia events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of hypophosphatemia by ATC classification and PT, grade (Grade 1, 2, 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs of hypophosphatemia by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.
- Rash, Hidradenitis, and Hair Follicle AEs (separately for Narrow and both Broad and Narrow Terms identified in Section 7.5.2)
    - Summary statistics for time to onset, duration of event, and time to resolution by event grade (Grade 1, 2, 3+) and overall
    - Summary statistics for time to onset of first event (days), duration of each event (days), and time from start of first event to resolution of all events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of events by ATC classification and PT, grade (Grade 1, 2, 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.

4.4.2.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for this study are defined in Protocol Section 8.3.6 and include the following groups and descriptions:

- Skin Rash (clinically significant Grade 2 and Grade ≥ 3, per CTCAE v.5)
    1. Maculopapular rash
    2. Pruritic rash
    3. Erythematous rash
    4. Folliculitis
    5. Hidradenitis suppurativa
- Elevated Liver Enzymes (reported as AESI if Grade ≥ 2, per CTCAE v.5)
    1. Aspartate Aminotransferase
    2. Alanine Aminotransferase
    3. Alkaline Phosphatase
- Electrolyte Insufficiency (Grade ≥ 3, per CTCAE v.5)
    1. Hypophosphatemia
    2. Hypokalemia
    3. Hypomagnesemia
- Drug Reactions (All grades)
    1. Allergic reaction
    2. Anaphylaxis
- Reproductive System Disorders (Grade ≥ 2, per CTCAE v.5)
    1. Amenorrhea
    2. Premature menopause / Primary ovarian insufficiency

Determination of whether an event is an AESI is based on investigator reported data. The incidence of AESI's will be summarized by AESI group and PT in tables and listed separately in participant data listings.

4.4.2.3. DT Specific Comorbidity

The incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity will be summarized by treatment arm. More details are provided in Section 4.3.3.14.

4.4.3. Clinical Safety Laboratory Assessments

Central results will be the primary results to be analyzed. However, if a subject has local lab results collected during a scheduled visit and does not have central laboratory results collected for a parameter, the local results will be included for analyses. If a subject has both central and local laboratory results collected for a lab parameter during a scheduled visit, only the central results will be included for analyses. Central laboratory results from unscheduled visits will be used in the baseline and worst post-baseline derivations only. Local unscheduled visits are excluded from derivations and summarized results.

The actual value and change from baseline will be summarized for each visit for clinical laboratory parameters (hematology, chemistry, coagulation, and hormones) by treatment arm and overall.

Laboratory results will also be summarized by maximum CTCAE grade as available. For lab tests with NCI – CTCAE classification, the shift from baseline to maximum (worst) post baseline grade will be tabulated. Shift tables will summarize the count and frequency of each CTC grade to the highest CTC grade on study and where appropriate for the lab test, will include shifts to abnormal high values or abnormal low values. Laboratory tests with bi-directional grades will be presented separately for each direction (e.g., hyperglycemia and hypoglycemia). For lab tests without NCI – CTCAE classifications, the shift from baseline to each post baseline visit as well as the shift to the worst value will be summarized using the lab range indicators (normal, high, or low).

Additional shift tables will be produced for ALT, AST, alkaline phosphatase, bilirubin, phosphorus, and creatine showing shifts from below normal range, within normal range, >1 to 2 × upper limit of normal range, >2 to 3 × upper limit of normal range, >3 to 5 × upper limit of normal range and > 5 × upper limit of normal range to the worst (highest) post baseline value. Analysis related to hormone levels will be presented according to sex and by childbearing potential for female participants.

Box and whiskers plots displaying the values over time by nominal visit will be produced for each lab test. Hormone parameters will be displayed separately by sex. Additionally, WOCBP and Women who are not of childbearing potentially will be displayed separately. WOCBP will also be displayed by OD status and treatment.

All laboratory results will be listed and laboratory tests with an abnormal result will be listed separately. A subset listing will be presented for all grade 3 or higher laboratory values. A listing of participants with AST or ALT > 3X ULN that occurred within 2 days of a bilirubin value >2 ULN will be presented.

Serum pregnancy testing data will be presented for each participant in a data listing.

4.4.4. Physical Examinations and Eastern Cooperative Oncology Group Performance Status

Physical examination abnormalities reported as AEs will be summarized along with other TEAEs.

Shift tables by treatment arm and overall will summarize the count and frequency for each shift of baseline ECOG performance status grade to worst post-baseline ECOG grade. Similar tables will be provided for shifts to better grades. The ECOG performance status grades are outlined in Table 7.

All physical examination findings and ECOG performance status results will be presented in data listings.

Table 7. Eastern Cooperative Oncology Group Performance Status Grades

Grade	Description
0+	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655

4.4.5. Electrocardiogram

The actual value and change from baseline at each time point will be summarized for 12-lead ECG parameters by treatment arm and overall. The triplicated 12-Lead ECG parameters include heart rate, PR, RR, QRS, QT and QTcF intervals. The data presented represents the average values from the triplicate ECGs.

Categorical groups of QTcF will be summarized as follows:

- Maximum post-baseline QTcF
  - ≤ 450 msec
  - > 450 and ≤ 480 msec
  - > 480 and ≤ 500 msec
  - > 500 msec
- Maximum change from baseline for QTcF
  - ≤ 30 msec
  - > 30 and ≤ 60 msec
  - > 60 msec

All ECG data will be included in a by-participant data listing. Listings will be provided for participants with abnormal or outlying values for QTcF and changes in QTcF.

4.4.6. Vital Signs

The actual value and change from baseline for all parameters (except height) will be summarized at each scheduled visit by treatment arm and overall.

Vital sign measurements will be presented for each participant in a data listing.

4.4.7. Concomitant Medications and Procedures

Concomitant medications and procedures will be coded using the WHO Drug Dictionary and are defined as any medication or procedure that did not end prior to first dose or start after the 30-day follow-up period. The handling of partial/missing start dates for concomitant therapies/medications are described in Appendix 7.2. PTs will be modified to be grouped as outlined in Appendix 7.4 to consolidate brand and generic medication names for the same active ingredient into a single line item to facilitate reporting of the same medication. Both the original and modified PTs will be included in the listings. Concomitant medications will be tabulated by anatomic therapeutic class (ATC) and modified PT by treatment arm and overall. In these tabulations, each participant will contribute only once to each ATC and modified PT regardless of number of uses.

Medications will be considered prior if they stopped before the first dose of study drug. Prior medications will be tabulated separately from concomitant medications.

All medications and procedures will be included in separate data listings; an identifier will be used to show whether a medication/procedure was prior or concomitant. Both original PT and modified PT will be presented on the listing.

4.5. Pharmacokinetic and Pharmacodynamic Analyses

A separate supplementary SAP will describe the PK parameters, PopPK/PD models, and analyses. Plasma pharmacokinetic collection dates, times, and concentration results will be displayed in a data listing.

5. CHANGES TO PLANNED ANALYSES

Notable changes from the protocol-defined statistical analyses compared to this statistical analysis plan are described below:

I. An interim analysis is no longer planned

II. "Change in tumor volume from baseline as assessed by MRI volumetric" has been moved from secondary to exploratory endpoint, per FDA comment

III. "Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks" has been moved from secondary to exploratory endpoint (as described in the PRO Addendum), due to duplications to other PROs.

IV. Duration of Response and Duration of Stable disease have been removed from the hierarchical testing of secondary endpoints as they are considered supportive of ORR.

V. Proportion of participants with improvement in BPI-SF API score at Cycle 10 has been removed from the hierarchical testing of secondary endpoints.

VI. Estimates of duration of response at Months 6, 12 and 24 have been added.

6. REFERENCES

Guo C, So Y, and Johnston G. Analyzing Interval-Censored Data with the ICLIFETEST Procedure. 2014. https://support.sas.com/resources/papers/proceedings14/SAS279-2014.pdf

Eisenhaur EA, Therasse P, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45(2):228-47.

European Medicines Agency. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. 2021 April 02 (Version 4.0).

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-556.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

The ICLIFETEST Procedure:
https://documentation.sas.com/doc/en/statug/15.2/statug_iclifetest_toc.htm

US Food and Drug Administration. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020 (Updated Jan 2021).

7. APPENDICES

7.1. Handling of Missing/Partial Dates for AEs

Adverse events with incomplete onset dates will be handled as follows for the purpose of determining treatment emergence.

If the start date is partially missing, the date will be compared to the start of administration of study drug and the end date of administration+30 days.

1. If the month and day are missing:
   - If the year of the event is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
   - If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
   - If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.
2. If the day is missing:
   - If the month and year are the same as the month of treatment, the onset date will be assigned to the date of treatment.
   - If the month and year are not the same as the month/year of treatment, then the onset day will be set to the first day of the month.

If the start date is completely missing and end date is not before the first dose of study drug, then the adverse event will be considered treatment emergent.

If the participant has died and the imputed date is later than the date of death, the date of death will be used.

7.2. Handling of Missing/Partial Dates for Concomitant Therapies/Medications

Concomitant therapies/medications with start dates that are completely or partially missing will be handled as follows for the propose of determining concomitance.

1. If the start date has the month and year but the day is missing, the therapy will be considered concomitant if the month and year are:
   a. On or after the month and year of the date of the first dose of study drug
   b. On or before the month and year of the date of the last dose of study drug plus 30 days
2. If the start date has the year, but the day and month are missing, the therapy will be considered concomitant if the year is:
   a. On or after the year of the date of the first dose of study drug

b. On or before the year of the date of the last dose of study drug plus 30 days.

3. If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is prior to the date of the first dose of study drug, then this therapy will not be considered concomitant.
4. If the start date of concomitant therapies is completely or partially missing and the stop date of concomitant therapies is on or after the date of the first dose of study drug, then the therapy will be considered concomitant.
5. If the start date and stop date of concomitant therapies are completely missing, then the therapy will be considered concomitant.

7.3. Handling of Missing Dates for Disease History and Prior Therapies

For the purpose of calculating time from diagnosis or most recent prior therapy to randomization, partial/missing dates for diagnosis and last prior therapy completion will be imputed as follows:

- If both day and month are missing and the year is prior to the year of screening, the imputed day and month will be 01 July.
- If both day and month are missing and the year is the same as the year of screening, the imputed date will be the middle point between 01 Jan of the year and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- If day is missing and the month and year are prior to the month and year of screening, the imputed date will be 15th day of the month.
- If day is missing and the month and year are the same as the month and year of screening, the imputed date will be the middle point between the first date of the month and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- No imputation will be performed if the year is missing.

7.4. Consolidated Medication Coding

Consistent with standard conventions for coding concomitant medications using WHO Drug preferred terms, the coded term for certain medications varies based on whether the reported verbatim term was a brand name or generic name. To facilitate data reporting for the same medication, the coded terms for brand and generic named medications will be consolidated in summary tables. WHO Drug preferred terms will be combined as outlined below. For all terms not listed, the original coded term will be used. Both the original and consolidated terms can be found in the datasets.

Original Term(s)	**New Term**
Morphine sulfate MS Contin	morphine sulfate
Loperamide Hydrochloride	Loperamide
Ketorolac Tromethamine	Ketorolac
Cyclobenzaprine Hydrochloride	Cyclobenzaprine
Venlafaxine Hydrochloride	Venlafaxine
Ciprofloxacin Hydrochloride	Ciprofloxacin
Levothyroxine Sodium	Levothyroxine
Prochlorperazine Edisylate Maleate	Prochlorperazine
Cetirizine hydrochloride	Cetirizine
Diphenhydramine Hydrochloride	Diphenhydramine
Valaciclovir Hydrochloride	Valacyclovir
Oxycodone Hydrochloride	Oxycodone
Pantoprazole sodium sesquihydrate	Pantoprazole
Macrogol 3350	Macrogol
Tramadol HCL	Tramadol
Metamizole Sodium	Metamazole
Imatinib mesylate	Imatinib
Sorafenib Tosilate	Sorafenib
Tegavivint	Tegatrabetan
Vinblastine Sulfate	Vinblastine
Vinorelbine tartrate	Vinorelbine

7.5. Preferred Terms for Adverse Event Analyses

7.5.1. Ovarian Dysfunction (OD)

The following list of preferred terms will serve to identify which WOCBP who are participating in studies of nirogacestat are of interest for additional analyses of the potential for nirogacestat to disrupt ovarian follicular cycling. Narrow terms are considered the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad."

Table 8. Broad Summary of Preferred Terms to Describe Ovarian Dysfunction in WOCBP

MedDRA Code	PT	HLT	SOC
10085424	Abnormal uterine bleeding	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10001928	Amenorrhoea[1]	Menstruation with decreased bleeding	Reproductive system and breast disorders
10002659	Anovulatory cycle	Female gonadal function disorders	Endocrine disorders
10075158	Anti-Muellerian hormone level decreased	Reproductive hormone analyses	Investigations
10075597	Antral follicle count low	Fertility analyses	Investigations
10003439	Artificial menopause[1]	Menopausal effects NEC	Reproductive system and breast disorders
10003693	Atrophic vulvovaginitis	Menopausal effects on the genitourinary tract	Reproductive system and breast disorders
10005104	Bleeding anovulatory	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10063241	Blood gonadotrophin releasing hormone increased	Hypothalamic analyses	Investigations
10005687	Blood oestrogen decreased	Reproductive hormone analyses	Investigations
10014757	Endometrial hypoplasia[1]	Uterine disorders NEC	Reproductive system and breast disorders
10065596	Female sex hormone level abnormal	Reproductive hormone analyses	Investigations
10071084	Follicle stimulating hormone deficiency	Anterior pituitary hypofunction	Endocrine disorders
10074538	Genital atrophy[1]	Reproductive tract disorders NEC (excl neoplasms)	Reproductive system and breast disorders
10060800	Hot flush	Peripheral vascular disorders NEC	Vascular disorders
10021033	Hypomenorrhoea	Menstruation with decreased bleeding	Reproductive system and breast disorders
10021928	Infertility female	Sexual function and fertility disorders NEC	Reproductive system and breast disorders
10062020	Infertility tests abnormal	Fertility analyses	Investigations
10071083	Luteinising hormone deficiency	Anterior pituitary hypofunction	Endocrine disorders
10067371	Menopausal depression[1]	Depressive disorders	Psychiatric disorders
10058825	Menopausal disorder[1]	Menopausal effects NEC	Reproductive system and breast disorders

MedDRA Code	PT	HLT	SOC
10027304	Menopausal symptoms[1]	Menopausal effects NEC	Reproductive system and breast disorders
10027327	Menstrual disorder	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10027336	Menstruation delayed	Menstruation with decreased bleeding	Reproductive system and breast disorders
10027339	Menstruation irregular	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10030229	Oestradiol decreased	Reproductive hormone analyses	Investigations
10030236	Oestriol decreased	Reproductive hormone analyses	Investigations
10030247	Oestrogen deficiency	Endocrine abnormalities of gonadal function NEC	Endocrine disorders
10030255	Oestrogens total urine decreased	Reproductive hormone analyses	Investigations
10063268	Oestrone decreased	Reproductive hormone analyses	Investigations
10030295	Oligomenorrhoea	Menstruation with decreased bleeding	Reproductive system and breast disorders
10033122	Ovarian atrophy[1]	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10033141	Ovarian disorder[1]	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10033165	Ovarian failure[1]	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10033310	Ovulation delayed	Female gonadal function disorders	Endocrine disorders
10067490	Ovulation disorder	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10036601	Premature menopause[1]	Menopausal effects NEC	Reproductive system and breast disorders
10067168	Ultrasound ovary abnormal	Reproductive organ and breast imaging procedures	Investigations
10047791	Vulvovaginal dryness	Vulvovaginal signs and symptoms	Reproductive system and breast disorders
10027308	Menopause[1]	Age related factors	Social circumstances

1. Term is both a broad and narrow term

7.5.2. Rash, Hidradenitis, Hair Follicle AEs

7.5.2.1. Rash

The following list of preferred terms is intended to identify patients participating in studies of nirogacestat who experienced adverse generalized rash-like skin events but excluding events due to the possible effects of nirogacestat on hair follicles. Narrow terms are considered to be the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad."

Table 9. Broad Summary of Preferred Terms to Describe Rash

MedDRA Code	PT	HLT	SOC
10037898	Rash vesicular	Rash vesicular	Rashes, eruptions and exanthems NEC
10037890	Rash scarlatiniform	Rash scarlatiniform	Rashes, eruptions and exanthems NEC
10057984	Rash rubelliform	Rash rubelliform	Rashes, eruptions and exanthems NEC
10037087	Pruritus	Pruritus	Pruritus NEC
10037884	Rash pruritic[1]	Rash pruritic	Rashes, eruptions and exanthems NEC
10037876	Rash papular[1]	Rash papular	Rashes, eruptions and exanthems NEC
10037870	Rash morbilliform[1]	Rash morbilliform	Rashes, eruptions and exanthems NEC
10050004	Rash maculovesicular	Rash maculovesicular	Rashes, eruptions and exanthems NEC
10037868	Rash maculo-papular[1]	Rash maculo-papular	Rashes, eruptions and exanthems NEC
10037867	Rash macular[1]	Rash macular	Rashes, eruptions and exanthems NEC
10015150	Erythema[1]	Erythema	Erythemas
10037855	Rash erythematous[1]	Rash erythematous	Rashes, eruptions and exanthems NEC
10037844	Rash[1]	Rash	Rashes, eruptions and exanthems NEC
10075807	Nodular rash[1]	Nodular rash	Rashes, eruptions and exanthems NEC
10056671	Mucocutaneous rash	Mucocutaneous rash	Rashes, eruptions and exanthems NEC
10037879	Rash papulosquamous[1]	Rash papulosquamous	Papulosquamous conditions
10037888	Rash pustular	Rash pustular	Skin structures and soft tissue infections
10037578	Pustule	Pustule	Skin structures and soft tissue infections
10064579	Exfoliative rash	Exfoliative rash	Exfoliative conditions
10040844	Skin exfoliation	Skin exfoliation	Exfoliative conditions
10012456	Dermatitis exfoliative generalised	Dermatitis exfoliative generalised	Exfoliative conditions
10012455	Dermatitis exfoliative	Dermatitis exfoliative	Exfoliative conditions
10047111	Vasculitic rash	Vasculitic rash	Skin vasculitides
10037857	Rash follicular[1]	Rash follicular	Pustular conditions
10012431	Dermatitis[1]	Dermatitis	Dermatitis and eczema
10082985	Erythrodermic atopic dermatitis	Erythrodermic atopic dermatitis	Exfoliative conditions
10012432	Dermatitis acneiform	Dermatitis acneiform	Acnes
10000496	Acne	Acne	Acnes
10000501	Acne conglobata	Acne conglobata	Acnes
10000503	Acne cystic	Acne cystic	Acnes
10000513	Acne pustular	Acne pustular	Skin structures and soft tissue infections
10013786	Dry skin	Dry skin	Dermal and epidermal conditions NEC

1. Term is both a broad and narrow term

7.5.2.2. Hidradenitis

The following list of preferred terms is intended to identify patients participating in studies of nirogacestat who experienced adverse events due to the possible effects of nirogacestat on hair follicles and sweat glands, e.g., hidradenitis. Narrow terms are considered to be the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad."

Table 10. Broad Summary of Preferred Terms to Describe Rash

MedDRA Code	PT	HLT	SOC
10020040	Hidradenitis[1]	Hidradenitis	Apocrine and eccrine gland disorders
10055027	Sweat gland infection	Sweat gland infection	Apocrine and eccrine gland disorders
10000318	Abscess sweat gland	Abscess sweat gland	Skin structures and soft tissue infections
10018736	Groin sinus excision	Groin sinus excision	Abdominal therapeutic procedures NEC
10050269	Groin abscess	Groin abscess	Infections NEC

1. Term is both a broad and narrow term

7.5.2.3. Hair Follicle AEs

The following list of preferred terms is intended to identify patients participating in studies of nirogacestat who experienced adverse skin events due to the possible effects of nirogacestat on hair follicles. Narrow terms are considered to be the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad".

Table 11. Broad Summary of Preferred Terms to Hair Follicle Adverse Events

MedDRA Code	PT	HLT	SOC
10066409	Staphylococcal skin infection	Staphylococcal skin infection	Staphylococcal infections
10052891	Skin bacterial infection	Skin bacterial infection	Bacterial infections NEC
10037637	Pyoderma streptococcal	Pyoderma streptococcal	Streptococcal infections
10037632	Pyoderma	Pyoderma	Skin structures and soft tissue infections
10017553	Furuncle[1]	Furuncle	Staphylococcal infections
10007247	Carbuncle	Carbuncle	Skin structures and soft tissue infections
10042343	Subcutaneous abscess	Subcutaneous abscess	Skin structures and soft tissue infections
10016936	Folliculitis[1]	Folliculitis	Bacterial infections NEC
10015988	Eyelid infection	Eyelid infection	Eye and eyelid infections
10057211	Eyelid folliculitis	Eyelid folliculitis	Skin structures and soft tissue infections
10015980	Eyelid boil	Eyelid boil	Eye and eyelid infections
10000297	Abscess of eyelid	Abscess of eyelid	Eye and eyelid infections
10030261	Oil acne	Oil acne	Acnes
10012432	Dermatitis acneiform	Dermatitis acneiform	Acnes
10000518	Acne varioliformis	Acne varioliformis	Acnes
10000511	Acne occupational	Acne occupational	Acnes
10000507	Acne infantile	Acne infantile	Acnes
10049141	Acne fulminans	Acne fulminans	Acnes
10000503	Acne cystic	Acne cystic	Acnes
10000502	Acne cosmetica	Acne cosmetica	Acnes
10000501	Acne conglobata	Acne conglobata	Acnes
10000496	Acne	Acne	Acnes
10037888	Rash pustular[1]	Rash pustular	Skin structures and soft tissue infections
10037578	Pustule[1]	Pustule	Skin structures and soft tissue infections
10020377	Hordeolum	Hordeolum	Eye and eyelid infections
10001760	Alopecia[1]	Alopecia	Alopecias
10073736	Diffuse alopecia[1]	Diffuse alopecia	Alopecias
10001767	Alopecia universalis[1]	Alopecia universalis	Alopecias
10001766	Alopecia totalis[1]	Alopecia totalis	Alopecias
10001761	Alopecia areata[1]	Alopecia areata	Alopecias

1. Term is both a broad and narrow term

8. CLINICAL STUDY REPORT APPENDICES

8.1. Statistical Tables, Figures and Listings to be Generated

The Table of Contents for full list of tables, figures and listings can be found in a separate document (NIR-DT-301 TFL Table of Contents.pdf).

STATISTICAL ANALYSIS PLAN FOR PATIENT-REPORTED OUTCOMES

An Addendum to NIR-DT-301 Statistical Analysis Plan (PRO Addendum)

Protocol NIR-DT-301

Protocol Number:	NIR-DT-301
Protocol Version and Date:	Amendment 5: 09 February 2021 Amendment 4: 07 July 2020 (not released to sites) Amendment 3: 27 January 2020 Amendment 2: 14 October 2019 Amendment 1: 28 November 2018 Original: 03 August 2018
Name of Test Drug:	PF-03084014 (nicoracetam)
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Placebo-Controlled
Sponsor:	SpringWorks Therapeutics 100 Washington Blvd. Stamford, CT 06902 United States
Sponsor Representative:	[redacted] Sponsor Biostatistician
Analysis Plan Date:	14 Oct 2021
Analysis Plan Version:	Final Version 1

APPROVAL SIGNATURE PAGE

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)
Sponsor:	SpringWorks Therapeutics 100 Washington Blvd Stamford, CT 06902 United States
Protocol Number:	NIR-DT-301
Document Date / Version:	14OCT2021 / Final Version 1

IQVIA Author:

[redacted]
IQVIA

Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

[redacted]
Sponsor Biostatistician
SpringWorks Therapeutics

Signature:_____

Date:_____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AP	Appetite loss
API	Average Pain Intensity
BPI-SF	Brief Pain Inventory Short Form
CDF	Cumulative Distribution Plot
CF	Cognitive functioning
CI	Confidence interval
CO	Constipation
CSR	Clinical Study Report
DI	Diarrhea
DT/AF	Desmoid Tumors/Aggressive Fibromatosis
DTIS	Desmoid Tumor Impact Scale
DTRF	Desmoid Tumor Research Tumor Foundation
DTSS	Desmoid Tumor Symptom Scale
DY	Dyspnea
EF	Emotional functioning
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FA	Fatigue
GHS/QoL	Global health status/Quality of life
GODDESS	GOunder/DTRF DEsmoid Symptom/Impact Scale
ITT	Intention-to-treat
LS	Least squares
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MMRM	Mixed model repeated measures
MNAR	Missing not at random
NRS	Numeric rating scale
NV	Nausea and vomiting
OLE	Open-label extension
PA	Pain
PF	Physical functioning
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PMM	Pattern mixture model
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System

Abbreviation	Definition
PROMIS PF	Patient-Reported Outcomes Measurement Information System Physical Function
QoL	Quality of life
RF	Role functioning
SAP	Statistical analysis plan
SF	Social functioning
SL	Insomnia

1. INTRODUCTION

This document is a patient-reported outcome (PRO) data analysis addendum to the statistical analysis plan (SAP) of NIR-DT-301, a Phase 3, randomized, double-blind, placebo-controlled study that compares the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

To evaluate desmoid tumor symptoms and impacts in patients with progressing DT/AF, the following PROs were collected in the study NIR-DT-301:

1. GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) Desmoid Symptom/Impact Scale (GODDESS)

2. Brief Pain Inventory Short form (BPI-SF)

3. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

4. Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a + 3 additional items from PROMIS item banks

5. Patient Global Impression of Severity (PGIS)

6. Patient Global Impression of Change (PGIC)

This addendum (PRO Addendum) is designed to outline the methods used in the analysis of the PRO data. Populations for analysis, data handling rules, statistical methods, and formats for data representation follow those specified in the NIR-DT-301 SAP, unless otherwise noted. The statistical analyses and summary tabulations described in this addendum will provide the basis for the results sections of the PRO analysis of the Clinical Study Report (CSR) for this trial.

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Design and Objectives

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF.

The primary objective of this study is:

- To determine the efficacy (as defined by progression-free survival) of nirogacestat in adult participants with progressing DT/AF

One of the secondary objectives of this study, relating to the PRO data, is:

- To evaluate desmoid tumor symptoms and impacts using the following PROs:
    - GODDESS
    - BPI-SF
    - EORTC QLQ-C30

Exploratory objectives of this study, relating to the PRO data, are:

- To evaluate desmoid tumor symptoms and impacts using the following PROs:
    - PROMIS PF short form 10a and 3 additional items from PROMIS item banks
    - PGIS
    - PGIC

Additional analyses where PRO based outcomes are correlated with clinical data are documented in the Main SAP (Section 4.3.3.9 Change in Symptoms by Exposure and Change in Tumor Size/Volume).

2.1.1. Synopsis of PRO Data Collection

This study will consist of two phases: the double-blind phase and the optional, open-label extension (OLE) phase.

The following PRO assessments will be conducted during the double-blind phase:

- Screening PRO assessment:
    - On Day 1 of the screening visit, participants will receive training by the site staff on how to use the home ePRO device and will include a practice questionnaire to be completed by the participant prior to leaving the site.

- Participants will then begin the screening PROs assessments that same day (more details outlined in Table 1).
- The PGIC is intentionally omitted from the screening PRO assessments.

- Baseline PRO assessment:
  - The baseline PRO assessments will begin 7 days prior to the Cycle 1 Day 1 visit (more details outlined in Table 1).
  - The PGIC is intentionally omitted from the baseline PRO assessments.
- Monthly PRO assessments are required throughout the study (Cycle 2, 3, 4 and on).

The following PRO assessments will be conducted during the OLE phase:

- Monthly PRO assessments are required for the first year (Cycle 2-12).
- Quarterly PRO assessments are required after the first year (Cycle 13, 16, 19 and on).

2.1.2. PRO Data Collection Procedures

The schedules of PRO assessments, as outlined in the study protocol, are provided in Table 1 (bouble blind phase) and Table 2 (OLE phase).

Table 1: Double-Blind Phase: PRO Assessment Administration Schedule (Reproduced from Table 1-1 of main SAP)

PROs	Screening PRO Assessments First 7 days of screening period							Baseline PRO Assessments 7 day prior to baseline visit							Base-line Visit	Monthly PRO Assessments 7 days prior to Cycle X/FU (X = Cycles 2, 3, 4 & on)							Cycle X/FU Visit
	d 1	d 2	d 3	d 4	d 5	d 6	d 7	d -7	d -6	d -5	d -4	d -3	d -2	d -1		d -7	d -6	d -5	d -4	d -3	d -2	d -1	
GODDESS (symptom scale)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
BPI-SF	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PROMIS							X							X								X	
GODDESS (impact scale)							X							X								X	
EORTC QLQ-C30							X							X								X	
PGIS							X							X								X	
PGIC																						X	

BPI = brief pain inventory; d = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; PGIC = patient global impression of change; PGIS = patient global impression of severity; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function

* PROMIS PF short form 10a plus 3 additional items from the PROMIS item bank.

Table 2: OLE Phase: PRO Assessment Administration Schedule (Reproduced from Table 1-2 of main SAP)

PROs	Monthly PRO Assessments *7 days prior to Cycle X (X = Cycles 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12)*							Cycle X	Quarterly PRO Assessments *7 day prior to Cycle X (X = Cycles 13, 16, 19, 22 & on)*							Cycle X	Follow-Up PRO Assessments *7 days prior to the FU visit*							FU Visit
	d -7	d -6	d -5	d -4	d -3	d -2	d -1		d -7	d -6	d -5	d -4	d -3	d -2	d -1		d -7	d -6	d -5	d -4	d -3	d -2	d -1	
GODDESS (symptom scale)	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
BPI-SF	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PROMIS*							X								X									X	
GODDESS (impact scale)							X								X									X	
EORTC QLQ-C30							X								X									X	
PGIS							X								X									X	
PGIC							X								X									X	

BPI = brief pain inventory; d = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; PGIS = patient global impression of severity; PRO = patient-reported outcome; PROMIS PF = Patient-Reported Outcomes Measurement Information System Physical Function

* PROMIS PF short form 10a plus 3 additional items from the PROMIS item bank.

2.1.3. Efficacy Endpoints

The primary efficacy endpoint of the study is progression free survival. It is documented in the Main SAP for DeFi clinical data analyses.

Secondary efficacy endpoints related to the PRO are as follows:

- Mean change from baseline at Cycle 10 in BPI-SF Average Pain Intensity (API) score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score
- Proportion of patients with improvement at Cycle 10 in BPI-SF API score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL)
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Physical Functioning
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Role Functioning

Exploratory endpoints related to PRO are as follows:

- Mean change from baseline at Cycle 10 in DTSS Pain Domain Score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 pain
- Mean change from baseline at Cycle 10 in PROMIS PF10a (sum score) and PF13 (sum score)
- Proportion of patients with improvement at Cycle 10 in DTSS Total Symptom Score and DTSS Pain Domain Score
- Proportion of patients with improvement at Cycle 10 in DTIS Physical Functioning Domain Score
- Time to first DT symptom improvement (using DTSS Total Symptom)
- Time to pain response (using DTSS Pain Domain Score)
- Time to first control of pain symptoms (using BPI-SF API)
- Time to pain response (using BPI-SF API)

2.2. PRO Measures

2.2.1. The GOunder/DTRF DEsmoid Symptom/Impact Scale (GODDESS)

The GODDESS tool was developed to measures signs and symptoms of desmoid tumors and their impact on patients' lives, using two separate scales – the DTSS and the DTIS. The DTSS consists of 11 items assessing the severity of key signs and symptoms, including pain, fatigue, swelling, muscle weakness, difficulty moving, and tumor location-specific signs/symptoms. The DTIS includes 17 items that measure the impact of the symptoms of DTSS on daily life. The items from the GODDESS tool are presented in Appendix 8.1.

2.2.1.1. Desmoid Tumor Symptom Scale (DTSS)

Items of DTSS are evaluated on an 11-point, numeric rating scale (NRS) from 0 to 10 to measure severity from "none" to "as bad as you can imagine," with a 24-hour recall period. The DTSS will also have daily total scores and weekly average scores computed for items 1-7 and 9-11. Item 8 refers to the location of the tumor and will not be includied in the scoring. Weekly average scores will be computed for the 7-day periods at Screening, Baseline, and the 7 days preceding each Cycle using the mean of the period's total daily scores but only if there are four or more days of assessments within that period.

The following daily scores will be derived for the DTSS for each day of completion:

- Total Symptom Score:
    - Mean of Pain items (Items 1-3) as a single score, then a mean of this with items 4-7)
        - $\frac{((Item\,1+Item\,2+Item\,3)/3)+Item\,4+Item\,5+Item\,6+Item\,7}{5}$
- Total Symptom Score -Average
    - Mean of Items 1-7
- Pain Domain Score
    - Mean of Items 1-3
- Extra-abdominal Symptoms Domain Score
    - Mean of Items 5-7
- Abdominal Symptoms Domain Score
    - Mean of Items 9-11

In the case of missing item-level data (not expected, as all items were administered electronically, and mandatory) participants will have a missing daily value.

Weekly summary scores will be created by averaging the daily scores over the 7 days period prior to each visit. A weekly score will be derived only if 4 or more out of 7 days period have non-missing scores.

Higher scores represent worse symptom severity. There is no total score for the DTSS.

2.2.1.2. Desmoid Tumor Impact Scale (DTIS)

Items of DTIS are evaluated either on an 11-point NRS to measure severity, or a 5-point Likert scale ranging from "none of the time" to "all of the time," to measure frequency with a 7-day recall period.

The following scores will be derived for the DTIS:

- Physical Function Domain Score
    - Mean of: Item 01 Moving, Item 02 Reaching (Freq), Item 06 Vigorous Activity, Item 07 Moderate Activity, Item 08 Accomplished Less
- Sleep Domain Score
    - Mean of: Item 03 Falling Asleep, Item 04 Comfortable in Bed, Item 05 Staying Asleep
- Emotion Domain Score
    - Mean of: Item 12 Fear Tests, Item 13 Fear Growth/Reoccurrence, Item 14 Hopelessness, Item 15 Anger, Item 16 Anxiety, Item 17 Frustration

In the case of missing item-level data (not expected as all items were electronically administered, and mandatory) participants will have a missing domain value.

Higher scores represent worse impact severity.

2.2.2. BPI Short Form (BPI-SF)

The BPI-SF is a measurement tool for assessing clinical pain and allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. The BPI-SF consists of 9 questions and utilizes an 11-point NRS from 0-10 (0 being "no pain" and 10 being "highest pain level") with a 24-hour recall period. BPI-SF is presented in Appendix 8.2.

The BPI-SF assesses pain at its "worst," "least," "average," and "now" (current pain) through four **pain severity** items (items 3, 4, 5 and 6) rated on 0–10 scale, with 0 = "no pain" and 10 = "pain as bad as you can imagine". To measure the average pain severity, a Pain Severity Subscale will be derived both daily and weekly. Daily score will be calculated as the average of the 4 items responses for each day, and the weekly score will be calculated as the average of the daily scores. All 4 questions must be answered for the daily average pain severity score to be computed. A weekly score will be derived only if 4 or more days out of 7 days period have non-

missing scores.

The BPI-SF also measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep through seven **pain interference** items (items 9A to 9G of question 9) rated on 0–10 scales (with 0 = "no interference" and 10 = "interferes completely"). To measure average pain interference, a Pain Interference Subscale will be derived both daily and weekly. Daily score will be calculated as the average of the 7 items responses for each day provided that 4 out of the 7 items have non-missing responses. The weekly score will be the average of the daily scores over the 7 days period prior to each visit. A weekly score will be derived only if 4 or more days out of 7 days period have non-missing scores.

In addition, Average Pain Intensity (API) will be calculated as the average of the daily BPI-SF Item 3 "Worst Pain in Past 24 hours" over the 7 day period prior to each visit. API will be derived only if 4 to 7 days have non-missing scores.

2.2.3. EORTC QLQ-C30

The EORTC QLQ-C30 is a quality of life (QoL) questionnaire used for assessing the health-related quality of life of cancer patients participating in international clinical trials. The items from the questionnaire are presented in Appendix 8.3.

EORTC QLQ-C30 version 3.0 will be used in this study, with a 7-day recall period. It consists of 30 questions, with all items scored 1 ("not at all") to 4 ("very much") except for the 2 items contributing to the global health status/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The recall period for each question is "during the past week". The instrument yields the following scales:

- GHS/QoL scale with 2 items
- 5 Functional scales :
    - Physical functioning (PF) with 5 items
    - Role functioning (RF) with 2 items
    - Emotional functioning (EF) with 4 items
    - Cognitive functioning (CF) with 2 items
    - Social functioning (SF) with 2 items
- 3 Symptom scales / single items :
    - Fatigue (FA) with 3 items
    - Nausea and vomiting (NV) with 2 items
    - Pain (PA) with 2 items

- Dyspnea (DY) , insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI) with 1 item each

- Financial impact of disease with 1 item .

The EORTC QLQ-C30 scale scores will be calculated using the EORTC QLQ-C30 Scoring Manual (Fayers, et al., 2001). Each of the scales will have a raw mean score computed as long as at least 50% of the scales' questions have responses. The raw score will be used in a scoring formula described below that will transform the raw score linearly onto a score of 0 to 100. Details on computing raw scores and transforming them are found in Appendix 8.3.

A higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms, i.e., a high score for a functional scale (PF, RF, EF, CF, SF) represents a high/healthy level of functioning, a high score for the GHS/QoL and FI represents a high QoL or less impact, but a high score for a symptom scale (FA, NV, PA, DY, SL, AP, CO, DI) represents a high level of symptomatology.

The financial impact domain will not be included in this PRO Addendum" to the DeFi Main SAP analysis as it is not related to symptoms, functioning or health-related quality of life, and therefore is not relevant for the context of the clinical trial.

2.2.4. PROMIS PF Short Form 10a + 3 Additional Items from PROMIS Item Bank

The PROMIS PF instruments measure self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands.

The PROMIS PF short form 10a version 2.0 will be used in this study with a 7-day recall period. The items from the questionnaire are presented in Appendix 8.4. This PRO assessment consists of 10 questions and was constructed with a focus on representing the range of the trait and the content of the item bank, as well as mapping the questions in the instrument to qualitative evidence of the physical function concepts important to patients. A total sum score will be computed using all 10 items. A T-score and standard error of the T-score associated with the total score will be assigned based on the short form conversion table accompanying the scale and found in Appendix 8.4. A higher PROMIS T-score represents more of the concept being measured. For positively-worded concepts like physical function, a T-score of 60 is one SD better than average, and a participant with a T-score of 40 is one SD worse than the average (PROMIS, s.f.).

To supplement the PROMIS PF short form 10a, 3 additional questions representing other elements of physical function found to be important to patients were selected from the PROMIS Physical Function, Upper Extremity, and Ability to Participate item banks.

- Additional item 1: "Are you able to bend or twist your back",
- Additional item 2: "Are you able to reach into a high cupboard",
- Additional item 3: "I have trouble doing my regular daily work around the house".

A total score for the PROMIS-PF 10a with these three additional items has been supported by further psychometric evaluation. Therefore, a PROMIS PF13 score will de derived as a sum score of all 13 items, provided that there are no missing items.

Due to limitations in available translations in some countries, the additional 3 questions were not available at all sites. As such, this analysis only applies to those participants with available data at baseline including PROMIS PF short for 10a plus the 3 additional questions.

2.2.5. Patient Global Impression of Severity (PGIS)

The PGIS is a single-item scale that evaluates the participant's perception of the overall severity of their desmoid related symptoms over the past week on a 4-point scale ranging from "none" to "severe.". The PGIS has a 7-day recall period. The scale is presented in Appendix 8.5.

2.2.6. Patient Global Impression of Change (PGIC)

The PGIC is a single-item scale that evaluates the participant's perception of the change in their overall status since the start of the study treatment on a 7-point scale ranging from "very much better" to "very much worse". The PGIC has a 7-day recall period. The scale is presented in Appendix 8.6.

3. SUBJECT POPULATION

3.1. Population Definitions

The Intent-to-Treat (ITT) Population will be evaluated and used for presentation and analysis of the PRO data. The ITT Population will consist of all participants who are enrolled and randomized to study treatment (nirogacestat or placebo). Participants will be analyzed according to the treatment they were randomized to and the strata to which they have been assigned. Participants who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

4. GENERAL STATISTICAL METHODS

4.1. General Methods

Continuous variables will be described by the number of participants, mean, median, standard deviation, minimum, and maximum. Categorical variables will be described by the number and percentage of participants within each category (with a category for missing data). Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. Additional conventions for presentation of study data are laid out in the main body of the NIR-DT-301 SAP and will be applied for the PRO analyses as appropriate.

Specific details on analysis of selected PRO measures are laid out in Section 5. All additional PRO measures, as well as all data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed as described in an exploratory PRO statistical analysis plan and reported separately.

4.2. Baseline Definitions

For all PRO analyses unless specified, baseline for the double-blind phase will be defined as the most recent measurement prior to the first administration of study drug.

For weekly summary scores of the GODDESS and the BPI-SF, the baseline score will be set as weekly average of the Baseline period (e.g., study days -7 through -1) if there are 4 or more days of assessments during that Baseline period. If there are less than 4 days of assessments during Baseline period, the baseline weekly score will be set to weekly average of the Screening visits' assessments, provided that there are 4 or more days of assessments during that period. Otherwise, it will be set as missing.

Baseline assessments of PGIC do not exist, as PGIC assessments are post-baseline only.

4.3. Adjustments for Covariates

In general, the stratification factor (as reported in randomization) will be included in the analysis of all PRO endpoints. In addition, longitudinal change from baseline models will account for the baseline scores.

4.4. Multiple Comparisons/Multiplicity

Multiplicity will be controlled via hierarchical testing method for the primary and secondary endpoints.

4.5. Subgroups

The longitudinal analysis of change from baseline in PRO endpoints and the time to pain response will be examined in selected subgroups as listed in Table 3.

Table 3 List of subgroups

Subgroup Name	Subgroup Levels
Primary tumor location as reported in randomization	Intra-abdominal
	Extra-abdominal
Baseline worst pain score	Uncontrolled (API > 4)
	Controlled (API ≤ 4)
Tumor focality	Multi-Focal Disease
	Single Tumor
Desmoid tumor treatment status	Treatment naïve, measurably progressing DT/AF that is deemed not amenable to surgery
	Recurrent, measurably progressing DT/AF following at least one line of therapy
	Refractory, measurably progressing DT/AF following at least one line of therapy
Sex	Male
	Female
Race	White
	Non-White
Geographic region	North America Sites
	Rest of World Sites
Age group	First age quartile
	Second age quartile
	Third age quartile
	Fourth age quartile
Ethnicity	Hispanic or Latino
	Not Hispanic or Latino

4.6. Withdrawals, Dropouts, Loss to Follow-up

Subjects who are withdrawn or discontinue from the study will not be replaced.

4.7. Missing, Unused, and Spurious Data

In case of missing items, the scale and total scores will be calculated as indicated in the scoring

manual for the PRO instrument for the existing instruments. For GODDESS all items for a given total or domain score should be present in order to create the total or domain score.

Weekly scores (GODDESS and BPI-SF) will be calculated only if there are 4 or more days of assessments with non-misiing data within the respective week.

It is anticipated that the great majority of missing data in this study will have a monotone pattern, meaning that once a participant has missing data at one visit, data will be missing at all subsequent visits. There may be some small amount of intermittent (non-monotone) missing data (when participant skips intermediate visits but returns for evaluations at subsequent visits).

Missing PRO data will be assumed to be missing at random (MAR) in general and will be analyzed using mixed model repeated measures (MMRM) analysis when appropriate. To address the possibility that missing data may not be MAR, sensitivity analysis with pattern mixture model (PMM) will be conducted.

4.8. Visit Windows

In line with the clinical SAP, no windowing conventions will be applied for the analysis of the PRO data. All data will be tabulated per the evaluation visit as recorded on the eCRF. In the case of multiple observations at a specific visit, the first observation will be used.

5. STUDY ANALYSES

5.1. Participant Disposition

The participant disposition by treatment arm for all PRO assessment timepoints in the double-blind phase will be provided:

- The number of participants with PRO assessment expected
- The number and % of participants with PRO assessment not expected due to progression
- The number and % of participants with PRO assessment not expected due to death
- The number and % of participants with PRO assessment not expected due to other reasons

The participant disposition by treatment arm per timepoint will also be provided graphically using bar charts.

A participant is expected to complete the PRO assessment as long as he/she is still alive and have not discontinued the study.

5.2. PRO Completion

PRO completion for all instruments will be examined at each timepoint in the double blind phase. Specifically, the following will be examined:

- Unadjusted completion rate at each timepoint will be calculated as the number of participants meeting at least the minimum requirements for scoring of each instrument divided by the number of participants in the ITT population.
- Adjusted completion rate at each timepoint will be calculated among participants who are expected to have PRO assessments.

For the adjusted completion rate described above, the following will be provided:

- The number and % of participants with all questions completed
- The number and % of participants meeting at least the minimum requirements for scoring of the instrument (see section 2.1.3)
- The number and % of participants with at least one question completed (for multi-item instruments)

The completion rates (both adjusted and unadjusted) by treatment arm per timepoint will also be provided graphically: This will be displayed using grouped bar charts with visit on the x-axis and percent completion on the y-axis. Groups will be defined by treatment arm.

5.3. Exploration of Missing Data

Tabular summaries for the percentage of participants by the reason for discontinuation of study treatment, as well as for withdrawal from the study, are provided in the clinical SAP and will not be repeated herein.

The number of participants with missing PRO data will be summarized by treatment arm and timepoint (all scheduled timepoints in the double blind and OLE phases). For this analysis, the frequency and percentage of:

- Informative missingness, versus
- Non-informative missingness

The denominator will be the number of participants in the ITT.

This will be tabulated over time by treatment arm for each PRO endpoint. Informative missingness will be based on discontinuation due to an adverse event or due to lack of efficacy.

A comprehensive evaluation of missing data may warrant a modification to the planned analysis Any such modification will be detailed in the CSR.

5.4. Descriptive Analyses

Descriptive statistics for the observed scores as well as change from baseline scores for all the scores resulting from the instruments described in Section 2.1.3 will be provided for the ITT population by treatment arm at each timepoint in the double blind. Graphical representation will be also provided for the observed scores, e.g., box and whisker plots will be presented by treatment arm at each timepoint.

A cumulative distribution function (CDF) plot showing a continuous plot of the absolute change from baseline during the study, with change scores presented on the x-axis and the cumulative percent of participants experiencing that change on the y-axis, will be presented by treatment arm at all post-baseline timepoints up to and including Cycle 10. The cumulative distribution plot will be produced for the following PRO scores:

- DTSS scores: Total Symptom Score, Pain Domain Score
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API
- EORTC QLQ-C30: GHS/QoL, PF, RF and PA
- PROMIS: PF10a (sum score) and PF13 (sum score).

In addition, the number and proportion of participants by pain severity at baseline will be reported by treatment arms. Pain severity at baseline will be defined using the API score at baseline and classified as follows:

- Controlled pain at baseline: is API ≤ 4
- Uncontrolled pain at baseline: if API >4.

5.5. Longitudinal Analysis of Change from Baseline

Change from baseline during the double-blind phase in PRO scores will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach (Brown & Prescott, 2006) (MMRM – Mixed Model Repeated Measures) in a primary analysis and a PMM (O'Kelly & Ratitch, 2014). in a sensitivity analysis. The PMM will be used to assess the robustness of the MMRM estimate with regard to missing data, when the MAR assumption is replaced by assumptions that are likely to be relatively less favorable to the experimental treatment.

The longitudinal analysis of change from baseline will include only the on-treatment assessments (thus excluding the unscheduled, EOT and follow-up visits).

5.5.1. Mixed Model Repeated Measures – Main Analysis

The primary objective of this analysis is to examine the treatment difference at Cycle 10. Data from a limited number of PRO assessments will used in case of substantial drop out (i.e., analysis will be limited to timepoints at which at least 10 participants have non-missing data in both treatment arms).

The response variable will be the change from baseline to each PRO assessment. The model will include the treatment arm and timepoint as fixed-effect categorical factors, the baseline PRO score and stratification factor (primary tumor location: intra-abdominal vs extra-abdominal) as fixed effects covariates, and the baseline x time and treatment x time interactions. Both main effects and the interaction terms will remain in the model, regardless of significance. The model will present least squares (LS) mean estimates, standard errors, 95% CIs, and p-values for mean changes from baseline to each visit.

A plot of the LS means accompanied by the 95% CI will be produced for each PRO measure by treatment arm.

The analysis will be conducted using PROC MIXED in SAS. The model will assume unstructured covariance among the within-participant repeated measurements. If the algorithm does not converge, a heterogeneous Toeplitz (the TOEPH option in SAS PROC MIXED) will be tried first and then AR(1) as a covariance structure to achieve convergence. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The normality and homoscedasticity of the residuals will be visually checked. Particularly, the scatter plot of the residuals versus the predicted endpoint values, and the histograms and the normal probability plots of the residuals, will be reviewed. Transformation of the raw data will be considered if the graphs of residuals clearly indicate heavily skewed and heteroscedastic distribution of errors.

The analysis will be performed on the ITT population. Separate models will be considered for each of the following PRO score:

- DTSS scores: Total Symptom Score, Pain Domain Score
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API
- EORTC QLQ-C30: GHS/QoL, PF, RF and PA
- PROMIS: PF10a (sum score) and PF13 (sum score).

For the subgroup examinations, a separate model will be considered for each subgroup listed in Section 4.5. The model will include the treatment arm, and timepoint as fixed-effect categorical factors, the baseline PRO score, stratification factor (primary tumor location: intra-abdominal vs extra-abdominal) and the subgroup as fixed effects covariates, and the baseline x time, treatment x time and treatment x subgroup interactions. Subgroup analyses will be run only for variables resulting in subgroups of at least 10 patients in each treatment arm. The following will be presented: least squares (LS) mean estimates for the overall treatment effect (across all timepoints), standard errors, 95% CIs, and p-values for mean changes from baseline to each visit, as well as the p-value for the treatment by subgroup interaction.

5.5.2. Pattern Mixture Model – Sensitivity Analysis

The MMRM assumes that the missing observations are MAR. To address the possibility of the data being missing not at random (MNAR) (e.g., non-ignorable missing data), a sensitivity analysis using a PMM with sequential modelling with multiple imputation and delta-adjustment will be used. Change from baseline to Cycle 10 in PRO scale will be analyzed using a pattern-mixture model using control-based approach by means of sequential modelling with multiple imputation as described by O'Kelly (O'Kelly & Ratitch, 2014). The results from this analysis will be used to judge the validity of the MAR assumption. Similar conclusions from MMRM and PMM would suggest that the results are not overly dependent on the assumptions of the primary analysis with regard to the missing data.

We distinguish between monotone and non-monotone missing values. Non-monotone missing values are values missing intermittently, where a participant may miss some PRO assessments but has PRO assessments for the same score later on. Monotone missing values are such that once a value is missing for a given score, no subsequent values for this score are available. Any given participant may have a combination of non-monotone and monotone missing values.

Non-monotone missing values are assumed to be MAR and will be multiply imputed using a Markov Chain Monte Carlo (MCMC) method of Proc MI in SAS. The imputation model will include the following:

- Treatment arms (nirogacestat or placebo)
- Stratification factors (primary tumor location:intra-abdominal vs extra-abdominal)
- Age (continuous)

- Gender (male or female)
- Geographic region (North America vs the rest of world)
- Desmoid Tumor Treatment Status (treatment naïve, recurrent or refractory)
- Any prior treatment (Yes vs No).

Non-monotone missing data will be imputed first, followed by the imputation of monotone missing data.

To impute monotone missing values, we define patterns depending on reason and timing of missingness as follows:

- **Pattern 1**: missing values before or at Cycle 10 due to participant's death;
- **Pattern 2**: missing values before or at Cycle 10 due to adverse events (AEs) or due to progression (clinical or radiographic);
- **Pattern 3**: missing values before or at Cycle 10 with missingness that does not satisfy conditions of patterns 1 to 2.

The patterns are mutually disjointed, i.e., each participant with monotone missing data belongs only to one pattern.

The following assumptions will be made for the missing data in each pattern:

For **pattern 1**, the worst score (e.g., 10 for DTSS Total Symptom Score) will be assigned as a penalty for unobservable values up Cycle 10 after participant's death. This will be applied to both treatment arms.

For **pattern 2**, control-based approach will be used for the nirogacestat arm. For the placebo arm, multiple imputation under MAR assumption wil be used.

For **pattern 3**, data will be assumed to be MAR in both treatment arms.

The imputation of monotone missing data will be done sequentially for each scheduled PRO assessment visit, k=k1,…,K (where K corresponds to Cycle 10) as follows:

a) Impute monotone missing data in pattern 1 at visit k as the worst possible score for the imputed PRO score.

b) For the pattern 3 and for pattern 2 placebo patients only, impute the monotone missing values at visit k using an MAR-based multiple imputation regression model (PROC MI option MONOTONE REG) including the effects for baseline covariates as listed for the imputation model of non-monotone missing data above and PRO values at each schedule assessment time point up to (k-1).

c) For the pattern 2 nirogacestat patients only, impute the monotone missing values at

visit k using multiple imputation regression model including the effects for baseline covariates as listed for the imputation model of non-monotone missing data above and PRO values at each schedule assessment time point up to (k-1); at this step we will include all patients from the nirogacestat arm with missing at visit k, plus patients from the placebo arm with visit k observed. We omit patients from the nirogacestat arm with outcomes observed at vist k. Multiple imputation will now estimate regression parameters for visit k using data from the placebo arm only. The imputed data for vist k for a patient from the nirogacestat arm will look similar to the imputed data for a similar patient from the placebo arm.

The above steps (a)-(c) are performed for each visit k, before proceeding with the imputations of the next visit (k+1).

A total of 50 multiply-imputed datasets will be created for each PRO. The random number generator seed for the imputation of non-monotone missing values using MCMC will be 5414, and the random seed for imputation of monotone missing values will be 5414+k, for k=1, 2, … for each sequential visit with monotone missing data.

The MMRM modeling with the identical setup as described above in Section 5.5.1 will be performed, i.e., at each timepoint and also overall across all timepoints giving each visit equal weight, for each imputed dataset.

The SAS MIAnalyze procedure will be used to combine the results of these analyses for the imputations. For a more detailed description of the implementation MNAR imputation, see Ratitch B and O'Kelly M (O'Kelly & Ratitch, 2014).

The treatment differences will be estimated from the final model with LS-means differences and using the REML method. The degrees of freedom will be estimated with the Kenward-Roger approximation. The LS mean treatment difference, 95% CI, and p-value will be presented. A plot of the LS means accompanied by the 95% CI will be produced by treatment and at each timepoint.

The analysis will be performed on the ITT population. Separate models will be considered for each of the following PRO scores:

- DTSS scores: Total Symptom Score
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API.
- EORTC QLQ-C30: GHS/QoL, PF and RF

5.6. Responder Analysis

To understand meaningful changes experienced by participants at Cycle 10 (during the double-blind phase only), the frequency of responders vs. non-responders on the selected PRO measures will be reported. These change groups will be defined using either established (e.g.-literature based) thresholds where they exist, or empirically- derived thresholds for the newly developed instrument or when no literature values were observed (see Table 4). The responder

analysis will be performed for the following measures:

- DTSS scores: Total Symptom Score, Pain Domain Score
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API.

For the GODDESS, as part of the psychometric analysis performed by IQVIA, clinically meaningful thresholds for improvement were also derived and will be used to define the responders and non-responders as described in Table 4 below.

Cut-off values of 30% or greater , or 2-point or greater change in numerical rating BPI-SF scores, have been proposed in the literature to detect clinically important improvements in cancer-related breakthrough pain and chronic pain states [(Farrar, et al., 2000) (Dworkin , et al., 2008)]. For this study, the value of 2 points will be used for API.

Table 4 Visit Responses for PRO Measures Based on Clinically Meaningful Thresholds

Instrument / Score	Primary threshold	Sensitivity 1 threshold	Sensitivity 2 threshold	Visit Response
GODDESS				
DTSS scores				
Total Symptom Score	CFB ≤ -1.4	CFB ≤ -1.0	CFB ≤ -1.7	Responder
	CFB > -1.4	CFB > -1.0	CFB > -1.7	Non-responder
Pain Domain Score	CFB ≤ -1.9	CFB ≤ -1.7	CFB ≤ -2.4	Responder
	CFB > -1.9	CFB > -1.7	CFB > -2.4	Non-responder
DTIS scores				
Physical Functioning Domain Score	CFB ≤ -0.8	CFB ≤ -0.6	CFB ≤ -1.0	Responder
	CFB > -0.8	CFB > -0.6	CFB > -1.0	Non-responder

CFB=change from baseline

The number and proportion of participants who are responders vs. non-responders (as defined in the table above) at Cycle 10 will be summarized at each post-baseline timepoint (the double-blind phase only) by treatment arm. The proportions will be derived in two ways. In the first analysis, the denominator will be the number of participants with non-missing data at Cycle 10. In a second analysis, the denominator will be the number of participants in the ITT population for whom a PRO is expected (i.e., including participants with missing data) at Cycle 10. Participants with missing data at Cycle 10 will be considered non-responders in this second analysis.

The proportion of participants who are responders vs non-responders in the second analysis described above will be presented graphically using bar charts.

In addition, for the DTSS Total Symptom Score, Pain Domain Score, and BPI-SF API, the symptom improvement rate will be defined as the number and proportion of participants who are responders at two or more consecutive timepoints during the double-blind period (see Table 4). This analysis will be performed only among those particpants with uncontrolled pain at

baseline (e.g., with a baseline API ≥4).

The improvement rate will be compared using a logistic regression stratified by primary tumor location (intra-abdominal or extra-abdominal). Additional covariates, such as age, gender, or disease characteristics, will also be examined and included as appropriate. The results of the analysis will be presented in terms of an odds ratio together with its associated 95% CI and two-sided p-value.

5.7. Time to Event Analysis

Time to event analyses will include all PRO assessments during the double-blind phase (thus any unscheduled and EOT visits) and will be performed separately for the following PRO scores:

- DTSS scores: Total Symptom Score, Pain Domain Score
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API.

The following time to event endpoints will be defined:

- Time to first DT symptom improvement (using DTSS Total Symptom)
- Time to first control of pain symptoms (using BPI-SF API)
- Time to pain response (using BPI-SF API, DTSS Pain Domain Score)
- Time to first improvement in functioning (using DTIS: Physical Functioning Domain Score)

Time to first DT symptom improvement will be defined as the duration of time from the date of randominzation to the date of the first time reduction of at least a **threshold** points in DT symptoms using the DTSS Total Symptom Score (the threshold value is provided in Table 4) as compared to the baseline score. Participants without observed symptom improvement at the time of analysis will be censored at the date of last available PRO assessment (i.e., date of the last non-missing value) on or before the analysis data cutoff date. Participants who were randomized but with no baseline or whose baseline scores do not allow for further improvement will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

Time to first control of pain symptoms will be defined as the time from randomization to first time the BPI-SF API score is ≤ 4. The analysis will include only those participants whose BPI-SF API baseline scores are > 4. Participants without observed control of pain symptoms at the time of analysis will be censored at the date of last pain assessment on or before the analysis data cutoff date. Participants who were randomized but with no baseline score will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

Time to pain response will be defined using the BPI-SF API and DTSS Pain Domain Score as follows: time to pain response is defined as the time from randomization to first occurence of pain response (as described in Table 4). Participants without observed pain response at the time of analysis will be censored at the date of last pain assessment on or before the analysis data cutoff date. Participants who were randomized but with no baseline or whose baseline scores do not allow for further reduction in pain will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

Time to first improvement in functioning will be defined using the DTIS Physical Functioning Domain Score as follows: time to clinically meaningful improvement is defined as the time from randomization to first occurrence of improvement (e.g., response, see Table 4). Participants without observed improvement at the time of analysis will be censored at the date of last PRO assessment on or before the analysis data cutoff date. Participants who were randomized but with no baseline or whose baseline scores do not allow for further improvement will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

For all time to event analyses, the time to event will be analyzed in months and will be presented by treatment arm. Kaplan-Meier curves will be presented. The hazard ratio (HR) and the 95% CI will be estimated using a Cox proportional hazards model controlling for stratification factor (primary tumor location [intra-abdominal or extra-abdominal]). Additional covariates, such as age, gender, or disease characteristics, will also be examined and included as appropriate.

A stratified log-rank test on the time to event will be performed using SAS PROC LIFETEST with method=PL option (Kaplan-Meier estimates, also known as the product-limit estimates). The HR with 2-sided 95% CI will be estimated from the stratified Cox proportional hazards model using SAS PHREG procedure with ties=EXACT option in the model. In this analysis, the baseline hazard function will be allowed to vary across strata; i.e., the MODEL statement will include the treatment arm variable as the only covariate and the STRATA statement will include the prespecified variable. The assumption of proportionality will be tested by producing plots of complementary log-log (event times) versus log(time).

Kaplan-Meier plots of the survival distribution function will be presented and include the number of participants at risk over time by treatment arm.

The time to pain response will also be examined in selected subgroups (see Section 4.5). For the subgroup examinations, separate unstratified Cox models will be employed for each subgroup listed in Section 4.5. The model will include the treatment arm, the subgroup and treatment x subgroup interaction. Subgroup analyses will be run only if at least 10 events occurred in one of the subgroups across treatment groups. The following will be presented for each subgroup: the number of patients, events and censored cases, the median time to event and the corresponding 95% CI , HR with 2-sided 95% CI and the p-value corresponding to the stratified log-rank test, as well as the p-value obtained from the unstratified Cox for the treatment by subgroup interaction.

6. CHANGES TO PLANNED ANALYSES

As of this date, there have been one notable change between the protocol-defined statistical analyses and those presented in this statistical analysis plan:

"Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks" has been moved from secondary to exploratory endpoint, due to duplications to other PROs.

7. REFERENCES

Brown, H. & Prescott, R., 2006. *Applied Mixed Models in Medicine.* s.l.:John Wiley and Sons Ltd.

Dworkin , R., Turk, D. & Wyrwich, K., 2008. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Pain,* Volume 9, pp. 105-21.

Farrar, J. et al., 2000. Defining the clinically important difference in pain outcome measures. *Pain,* Volume 88, pp. 287-94.

Fayers, P. et al., 2001. EORTC QLQ-C30 Scoring Manual (3rd ed.). *EORTC.*

O'Kelly, M. & Ratitch, B., 2014. *Clinical Trials with Missing Data: A Guide for Practitioners..* s.l.:John Wiley & Sons Ltd.

PROMIS, n.d. Physical functioning: A brief guide to the PROMIS Physical Function instruments. *Patient-Reported Outcomes Measurement Information System (PROMIS).*

8. APPENDICES

8.1. The GOunder/DTRF DEsmoid Symptom/Impact Scale (GODDESS)

8.1.1. Items of Desmoid Tumor Impact Scale (DTIS)

Item #	Question	Scale	Range
1	During the past 7 days How often have you had difficulty moving (for example twisting or bending) near your tumor?	5	None - All the time
2	How often have you had difficulty with reaching up, such as reaching shelves that were above your head?	5	None - All the time
3	How often have you had trouble falling asleep?	5	None - All the time
4	How often have you had difficulty getting comfortable in bed?	5	None - All the time
5	How often have you had trouble staying asleep at night?	5	None - All the time
6	How often have you had difficulty doing vigorous activities (such as running, lifting heavy objects, or participating in strenuous sports)?	5	None - All the time
7	How often have you had difficulty doing moderate activities (such as pushing a vacuum cleaner, playing with children, or taking a long walk)?	5	None - All the time
8	How often have you accomplished less than you would like when doing work or other regular daily activities?	5	None - All the time
9	How often have you avoided people because of the way you feel about your appearance?	5	None - All the time
10	What was your worst difficulty with reaching up, such as reaching shelves that were above your head?	11	0 - 10
11	Have you been dissatisfied about your appearance?	11	0 - 10
12	How much fear of future diagnostic tests did you have?	11	0 - 10
13	How much fear of recurrence / growth of your desmoid tumor(s) did you have?	11	0 - 10
14	How much hopelessness did you have?	11	0 - 10
15	How much anger did you have?	11	0 - 10
16	How much anxiety did you have?	11	0 - 10
17	How much frustration did you have?	11	0 - 10

8.1.2. Items of Desmoid Tumor Symptom Scale (DTSS)

Item #	Question	Scale	Range	Note
	During the past 24 hours			
1	How bad was your worst feeling of pain?	11	0 - 10	
2	How bad was your worst feeling of dull pain?	11	0 - 10	
3	How bad was your worst feeling of shooting pain?	11	0 - 10	
4	How bad was your worst feeling of fatigue?	11	0 - 10	
5	What was your worst swelling around your tumor(s)?	11	0 - 10	
6	What was your worst muscle weakness around your tumor(s)?	11	0 - 10	
7	At its worst, how difficult was moving (for example twisting or bending) near your tumor(s)?	11	0 - 10	
8	Please indicate the location(s) of your desmoid tumor(s). Select all that apply.			Gate Q for Q9 - Q11
9	How bad was your worst feeling of abdominal pain?	11	0 - 10	If Abdominal Wall in Q8
10	How bad was your worst feeling of nausea?	11	0 - 10	If Abdominal Wall in Q8
11	How bad was your worst feeling of fullness after beginning to eat?	11	0 - 10	If Abdominal Wall in Q8

8.2. BPI Short Form

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

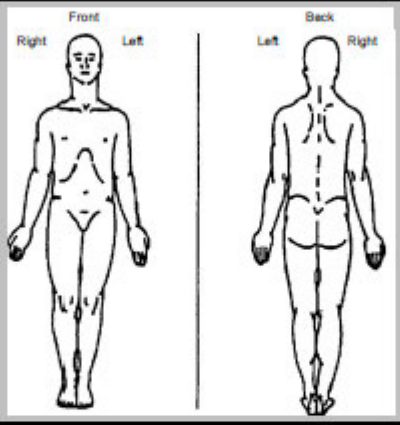
Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ___/___/____ Time: _____
Name: _____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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8.3. EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Scoring the EORTC QLQ-C30 version 3.0

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS-1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

8.4. PROMIS

8.4.1. PROMIS PF Short Form 10a

PROMIS® Item Bank v2.0 – Physical Function – Short Form 10a

Physical Function – Short Form 10a

Please respond to each question or statement by marking one box per row.

		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36r1	Does your health now limit you in walking more than a mile (1.6 km)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Cannot do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA10r1	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA56	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45r1	Are you able to sit on and get up from the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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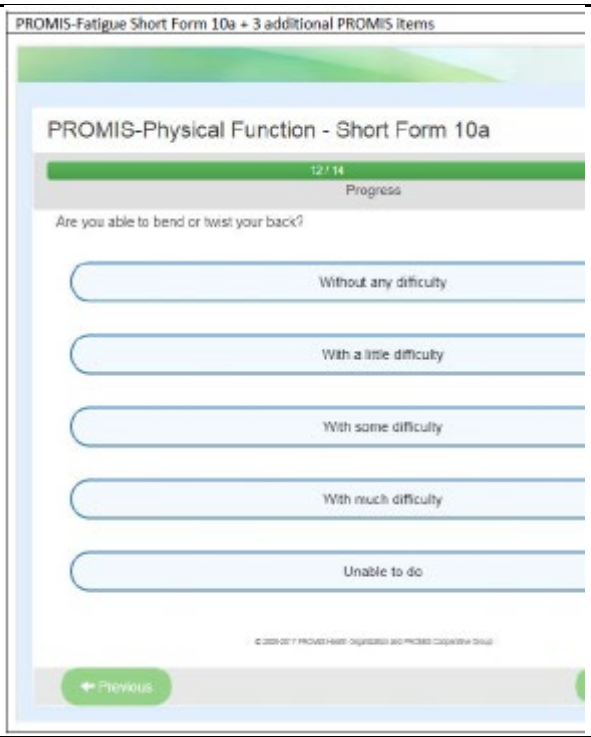
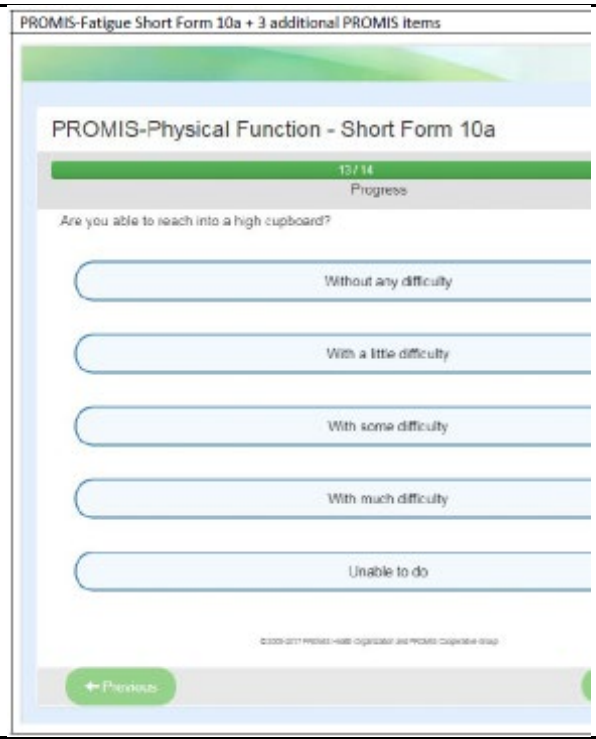
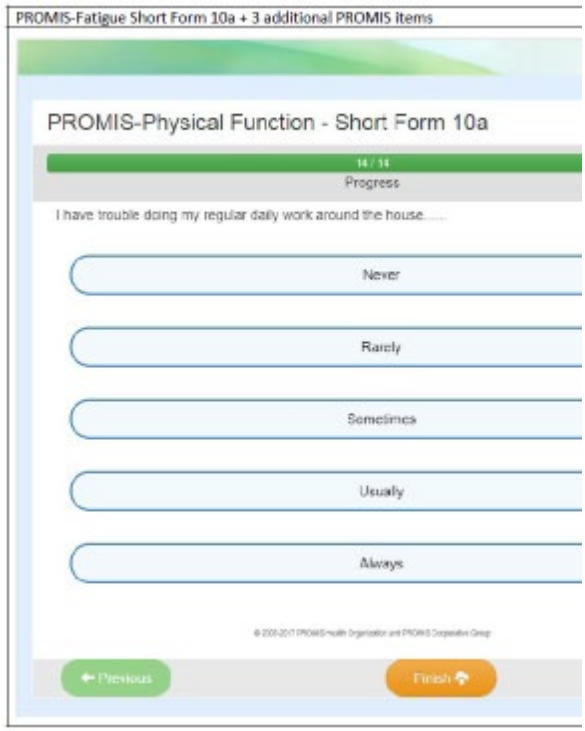
8.4.2. PROMIS PF Short Form 10a Look-Up Table

Adult v2.0 – Physical Function 10a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
10	13.5	3.6
11	16.6	2.8
12	18.3	2.7
13	19.7	2.5
14	20.9	2.4
15	22.1	2.3
16	23.1	2.2
17	24.1	2.2
18	25.0	2.1
19	26.0	2.0
20	26.9	2.0
21	27.7	1.9
22	28.6	1.9
23	29.4	1.9
24	30.2	1.8
25	31.0	1.8
26	31.8	1.8
27	32.5	1.8
28	33.3	1.7
29	34.0	1.7
30	34.8	1.7
31	35.5	1.7
32	36.3	1.7
33	37.0	1.7
34	37.8	1.7
35	38.5	1.8
36	39.3	1.8
37	40.1	1.8
38	40.9	1.9
39	41.7	1.9
40	42.6	1.9
41	43.5	2.0
42	44.4	2.1
43	45.5	2.1
44	46.6	2.3
45	47.9	2.5
46	49.4	2.8
47	51.2	3.2
48	53.4	3.6
49	55.8	3.9
50	61.9	5.9
*SE = Standard Error on T-score metric		

8.4.3. 3 Additional Items from PROMIS Item Banks







8.5. PGIS

Please choose the response below that best describes the severity of your desmoid related symptoms over the past week.

□ None

□ Mild

□ Moderate

□ Severe

8.6. PGIC

Please choose the response below that best describes the overall change in your general state of health since you started taking your study medication.

□ Very much Better

□ Moderately Better

□ A Litter Better

□ No Change

□ A Little Worse

□ Moderately Worse

□ Very much Worse

STATISTICAL ANALYSIS PLAN FOR PATIENT-REPORTED OUTCOMES

An Addendum to NIR-DT-301 Statistical Analysis Plan (PRO Addendum)

Protocol NIR-DT-301

Protocol Number:	NIR-DT-301
Protocol Version and Date:	Amendment 5: 09 February 2021 Amendment 4: 07 July 2020 (not released to sites) Amendment 3: 27 January 2020 Amendment 2: 14 October 2019 Amendment 1: 28 November 2018 Original: 03 August 2018
Name of Test Drug:	PF-03084014 (nirogacestat)
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Placebo-Controlled
Sponsor:	SpringWorks Therapeutics 100 Washington Blvd. Stamford, CT 06902 United States
Sponsor Representative:	[redacted] Sponsor Biostatistician
Analysis Plan Date:	05 Apr 2022
Analysis Plan Version:	Final Version 2

APPROVAL SIGNATURE PAGE

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)
Sponsor:	SpringWorks Therapeutics 100 Washington Blvd Stamford, CT 06902 United States
Protocol Number:	NIR-DT-301
Document Date / Version:	05 Apr 2022 / Final Version 2

IQVIA Author:

[redacted]
IQVIA

Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

[redacted]
Sponsor Biostatistician
SpringWorks Therapeutics

Signature:_____

Date:_____

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	14Oct2021	[redacted]	Not Applicable – First Version
2.0	12Jan2022	[redacted]	Clarifications added in response to FDA comments and to enhance readability. Specifically, the following key modifications were performed: • statistical test was added for the proportion of patients with improvement at Cycle 10 in section 5.6 • clarification on the seed used in the multiple imputation was added in section 5.5.2 • clarified that the formal statistical testing on PRO-related endpoints is conducted at the 1-sided, 0.025 level of significance. • Supplementary analysis added where GODDESS Total Symptom Score is derived excluding item 2 (dull pain) and item 3 (shooting pain) • Proportion of participants with improvement in BPI-SF API score at Cycle 10 has been removed from the hierarchical testing of secondary endpoints and added as an exploratory endpoint.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AP	Appetite loss
API	Average Pain Intensity
BPI-SF	Brief Pain Inventory Short Form
CDF	Cumulative Distribution Function
CF	Cognitive functioning
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CO	Constipation
CSR	Clinical Study Report
DI	Diarrhea
DT/AF	Desmoid Tumors/Aggressive Fibromatosis
DTIS	Desmoid Tumor Impact Scale
DTRF	Desmoid Tumor Research Foundation
DTSS	Desmoid Tumor Symptom Scale
DY	Dyspnea
EF	Emotional functioning
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FA	Fatigue
GHS/QoL	Global health status/Quality of life
GODDESS	GOunder/DTRF DEsmoid Symptom/Impact Scale
HR	Hazard Ratio
ITT	Intention-to-treat
LS	Least squares
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MMRM	Mixed model repeated measures
MNAR	Missing not at random
NDA	New Drug Application
NRS	Numeric rating scale
NV	Nausea and vomiting
OLE	Open-label extension
OR	Odds ratio
PA	Pain
PF	Physical functioning
PGIC	Patient Global Impression of Change

Abbreviation	Definition
PGIS	Patient Global Impression of Severity
PMM	Pattern mixture model
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMIS PF	Patient-Reported Outcomes Measurement Information System Physical Function
QoL	Quality of life
REML	restricted maximum likelihood
RF	Role functioning
SAP	Statistical analysis plan
SF	Social functioning
SL	Insomnia

1. INTRODUCTION

This document is a patient-reported outcome (PRO) data analysis addendum to the statistical analysis plan (SAP) of NIR-DT-301, a Phase 3, randomized, double-blind, placebo-controlled study that compares the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

To evaluate desmoid tumor symptoms and impacts in patients with progressing DT/AF, the following PROs were collected in the study NIR-DT-301:

1. GOunder/Desmoid Tumor Research Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS)

2. Brief Pain Inventory Short form (BPI-SF)

3. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

4. Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a + 3 additional items from PROMIS item banks

5. Patient Global Impression of Severity (PGIS)

6. Patient Global Impression of Change (PGIC)

This addendum (PRO Addendum) is designed to outline the methods used in the analysis of the PRO data. Populations for analysis, data handling rules, statistical methods, and formats for data representation follow those specified in the NIR-DT-301 SAP, unless otherwise noted. The statistical analyses and summary tabulations described in this addendum will provide the basis for the results sections of the PRO analysis of the Clinical Study Report (CSR) for this trial.

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Design and Objectives

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF.

The primary objective of this study is:

- To determine the efficacy (as defined by progression-free survival) of nirogacestat in adult participants with progressing DT/AF

One of the secondary objectives of this study, relating to the PRO data, is:

- To evaluate desmoid tumor symptoms and impacts using the following PROs:
    - GODDESS
    - BPI-SF
    - EORTC QLQ-C30

Exploratory objectives of this study, relating to the PRO data, are:

- To evaluate desmoid tumor symptoms and impacts using the following PROs:
    - PROMIS PF short form 10a and 3 additional items from PROMIS item banks
    - PGIS
    - PGIC

Additional analyses where PRO based outcomes are correlated with clinical data are documented in the Main SAP (Section 4.3.3.9 Change in Symptoms by Exposure and Change in Tumor Size/Volume).

2.1.1. Synopsis of PRO Data Collection

This study will consist of two phases: the double-blind phase and the optional, open-label extension (OLE) phase.

The following PRO assessments will be conducted during the double-blind phase:

- Screening PRO assessment:
    - On Day 1 of the screening visit, participants will receive training by the site staff on how to use the home ePRO device and will include a practice questionnaire to be completed by the participant prior to leaving the site.

- Participants will then begin the screening PROs assessments that same day (more details outlined in Table 1).
- The PGIC is intentionally omitted from the screening PRO assessments.

- Baseline PRO assessment:
  - The baseline PRO assessments will begin 7 days prior to the Cycle 1 Day 1 visit (more details outlined in Table 1).
  - The PGIC is intentionally omitted from the baseline PRO assessments.
- Monthly PRO assessments are required throughout the study (Cycle 2, 3, 4 and on).

The following PRO assessments will be conducted during the OLE phase:

- Monthly PRO assessments are required for the first year (Cycle 2-12).
- Quarterly PRO assessments are required after the first year (Cycle 13, 16, 19 and on).

2.1.2. PRO Data Collection Procedures

The schedules of PRO assessments, as outlined in the study protocol, are provided in Table 1 (double-blind phase) and Table 2 (OLE phase).

Table 1: Double-Blind Phase: PRO Assessment Administration Schedule (Reproduced from Table 1-1 of main SAP)

PROs	Screening PRO Assessments First 7 days of screening period							Baseline PRO Assessments 7 day prior to baseline visit							Base-line Visit	Monthly PRO Assessments 7 days prior to Cycle X/FU (X = Cycles 2, 3, 4 & on)							Cycle X/FU Visit
	d 1	d 2	d 3	d 4	d 5	d 6	d 7	d -7	d -6	d -5	d -4	d -3	d -2	d -1		d -7	d -6	d -5	d -4	d -3	d -2	d -1	
GODDESS (symptom scale)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
BPI-SF	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PROMIS							X							X								X	
GODDESS (impact scale)							X							X								X	
EORTC QLQ-C30							X							X								X	
PGIS							X							X								X	
PGIC																						X	

BPI = brief pain inventory; d = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; PGIC = patient global impression of change; PGIS = patient global impression of severity; PRO = patient-reported outcome; PROMIS PF= Patient-Reported Outcomes Measurement Information System Physical Function

* PROMIS PF short form 10a plus 3 additional items from the PROMIS item bank.

Table 2: OLE Phase: PRO Assessment Administration Schedule (Reproduced from Table 1-2 of main SAP)

PROs	Monthly PRO Assessments *7 days prior to Cycle X (X = Cycles 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12)*							Cycle X	Quarterly PRO Assessments *7 day prior to Cycle X (X = Cycles 13, 16, 19, 22 & on)*							Cycle X	Follow-Up PRO Assessments *7 days prior to the FU visit*							FU Visit
	d -7	d -6	d -5	d -4	d -3	d -2	d -1		d -7	d -6	d -5	d -4	d -3	d -2	d -1		d -7	d -6	d -5	d -4	d -3	d -2	d -1	
GODDESS (symptom scale)	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
BPI-SF	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PROMIS*							X								X									X	
GODDESS (impact scale)							X								X									X	
EORTC QLQ-C30							X								X									X	
PGIS							X								X									X	
PGIC							X								X									X	

BPI = brief pain inventory; d = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FU = follow-up; GODDESS = GOunder/DTRF DEsmoid Symptom/Impact Scale; PGIS = patient global impression of severity; PRO = patient-reported outcome; PROMIS PF = Patient-Reported Outcomes Measurement Information System Physical Function

* PROMIS PF short form 10a plus 3 additional items from the PROMIS item bank.

2.1.3. Efficacy Endpoints

The primary efficacy endpoint of the study is progression free survival. It is documented in the Main SAP for DeFi clinical data analyses.

Secondary efficacy endpoints related to the PRO are as follows:

- Mean change from baseline at Cycle 10 in BPI-SF Average Pain Intensity (API) score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL)
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Physical Functioning
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Role Functioning

Exploratory endpoints related to PRO are as follows:

- Mean change from baseline at Cycle 10 in DTSS Pain Domain Score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 pain
- Mean change from baseline at Cycle 10 in PROMIS PF10a (sum score) and PF13 (sum score)
- Proportion of participants with improvement at Cycle 10 in DTSS Total Symptom Score and DTSS Pain Domain Score
- Proportion of participants with improvement at Cycle 10 in DTIS Physical Functioning Domain Score
- Proportion of participants with improvement at Cycle 10 in BPI-SF API score
- Time to first DT symptom improvement (using DTSS Total Symptom)
- Time to pain response (using DTSS Pain Domain Score)
- Time to first control of pain symptoms (using BPI-SF API)
- Time to pain response (using BPI-SF API)

2.2. PRO Measures

2.2.1. The GOunder/DTRF DEsmoid Symptom/Impact Scale (GODDESS)

The GODDESS tool was developed to measures signs and symptoms of desmoid tumors and their impact on patients' lives, using two separate scales – the DTSS and the DTIS. The DTSS consists of 11 items assessing the severity of key signs and symptoms, including pain, fatigue, swelling, muscle weakness, difficulty moving, and tumor location-specific signs/symptoms. The DTIS includes 17 items that measure the impact of the symptoms of DTSS on daily life. The items from the GODDESS tool are presented in Appendix 8.1.

2.2.1.1. Desmoid Tumor Symptom Scale (DTSS)

Items of DTSS are evaluated on an 11-point, numeric rating scale (NRS) from 0 to 10 to measure severity from "none" to "as bad as you can imagine," with a 24-hour recall period. The DTSS will also have daily total scores and weekly average scores computed for items 1-7 and 9-11. Item 8 refers to the location of the tumor and will not be includied in the scoring. Weekly average scores will be computed for the 7-day periods at Screening, Baseline, and the 7 days preceding each Cycle using the mean of the period's total daily scores but only if there are four or more days of assessments within that period.

The following daily scores will be derived for the DTSS for each day of completion:

- Total Symptom Score:
  - Mean of Pain items (Items 1-3) as a single score, then a mean of this with items 4-7)
    - $\frac{((Item\,1+Item\,2+Item\,3)/3)+Item\,4+Item\,5+Item\,6+Item\,7}{5}$
- Total Symptom Score-5 Items:
  - Mean of items 1, 4, 5, 6 and 7
- Total Symptom Score -Average
  - Mean of Items 1-7
- Pain Domain Score
  - Mean of Items 1-3
- Extra-abdominal Symptoms Domain Score
  - Mean of Items 5-7
- Abdominal Symptoms Domain Score
  - Mean of Items 9-11

In the case of missing item-level data (not expected, as all items were administered electronically, and mandatory) participants will have a missing daily value.

Weekly summary scores will be created by averaging the daily scores over the 7 days period prior to each visit. A weekly score will be derived only if 4 or more out of 7 days period have non-missing scores. The weekly summary score will be used in analyses. If no weekly summary score is calculable, the participant will have data considered as missing at that visit.

Higher scores represent worse symptom severity. There is no total score for the DTSS.

2.2.1.2. Desmoid Tumor Impact Scale (DTIS)

Items of DTIS are evaluated either on an 11-point NRS to measure severity, or a 5-point Likert scale ranging from "none of the time" to "all of the time," to measure frequency with a 7-day recall period.

The following scores will be derived for the DTIS:

- Physical Function Domain Score
    - Mean of: Item 01 Moving, Item 02 Reaching (Freq), Item 06 Vigorous Activity, Item 07 Moderate Activity, Item 08 Accomplished Less
- Sleep Domain Score
    - Mean of: Item 03 Falling Asleep, Item 04 Comfortable in Bed, Item 05 Staying Asleep
- Emotion Domain Score
    - Mean of: Item 12 Fear Tests, Item 13 Fear Growth/Reoccurrence, Item 14 Hopelessness, Item 15 Anger, Item 16 Anxiety, Item 17 Frustration

In the case of missing item-level data (not expected as all items were electronically administered, and mandatory) participants will have a missing domain value.

Higher scores represent worse impact severity.

2.2.2. BPI Short Form (BPI-SF)

The BPI-SF is a measurement tool for assessing clinical pain and allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. The BPI-SF consists of 9 questions and utilizes an 11-point NRS from 0-10 (0 being "no pain" and 10 being "highest pain level") with a 24-hour recall period. BPI-SF is presented in Appendix 8.2.

The BPI-SF assesses pain at its "worst," "least," "average," and "now" (current pain) through four **pain severity** items (items 3, 4, 5 and 6) rated on 0–10 scale, with 0 = "no pain" and 10 = "pain as bad as you can imagine". To measure the average pain severity, a Pain Severity

Subscale will be derived both daily and weekly. Daily score will be calculated as the average of the 4 items responses for each day, and the weekly score will be calculated as the average of the daily scores. All 4 questions must be answered for the daily average pain severity score to be computed. A weekly score will be derived only if 4 or more days out of 7 days period have non-missing scores.

The BPI-SF also measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep through seven **pain interference** items (items 9A to 9G of question 9) rated on 0–10 scales (with 0 = "no interference" and 10 = "interferes completely"). To measure average pain interference, a Pain Interference Subscale will be derived both daily and weekly. Daily score will be calculated as the average of the 7 items responses for each day provided that 4 out of the 7 items have non-missing responses. The weekly score will be the average of the daily scores over the 7 days period prior to each visit. A weekly score will be derived only if 4 or more days out of 7 days period have non-missing scores.

In addition, Average Pain Intensity (API) will be calculated as the average of the daily BPI-SF Item 3 "Worst Pain in Past 24 hours" over the 7 day period prior to each visit. API will be derived only if 4 to 7 days have non-missing scores.

2.2.3. EORTC QLQ-C30

The EORTC QLQ-C30 is a quality of life (QoL) questionnaire used for assessing the health-related quality of life of cancer patients participating in international clinical trials. The items from the questionnaire are presented in Appendix 8.3.

EORTC QLQ-C30 version 3.0 will be used in this study, with a 7-day recall period. It consists of 30 questions, with all items scored 1 ("not at all") to 4 ("very much") except for the 2 items contributing to the global health status/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The recall period for each question is "during the past week". The instrument yields the following scales:

- GHS/QoL scale with 2 items
- 5 Functional scales :
    - Physical functioning (PF) with 5 items
    - Role functioning (RF) with 2 items
    - Emotional functioning (EF) with 4 items
    - Cognitive functioning (CF) with 2 items
    - Social functioning (SF) with 2 items
- 3 Symptom scales / single items :
    - Fatigue (FA) with 3 items

- Nausea and vomiting (NV) with 2 items
- Pain (PA) with 2 items
- Dyspnea (DY) , insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI) with 1 item each

- Financial impact of disease with 1 item .

The EORTC QLQ-C30 scale scores will be calculated using the EORTC QLQ-C30 Scoring Manual (Fayers, et al., 2001). Each of the scales will have a raw mean score computed as long as at least 50% of the scales' questions have responses. The raw score will be used in a scoring formula described below that will transform the raw score linearly onto a score of 0 to 100. Details on computing raw scores and transforming them are found in Appendix 8.3.

A higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms, i.e., a high score for a functional scale (PF, RF, EF, CF, SF) represents a high/healthy level of functioning, a high score for the GHS/QoL and FI represents a high QoL or less impact, but a high score for a symptom scale (FA, NV, PA, DY, SL, AP, CO, DI) represents a high level of symptomatology.

The financial impact domain will not be included in this PRO Addendum to the DeFi Main SAP analysis as it is not related to symptoms, functioning or health-related quality of life, and therefore is not relevant for the context of the clinical trial.

2.2.4. PROMIS PF Short Form 10a + 3 Additional Items from PROMIS Item Bank

The PROMIS PF instruments measure self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands.

The PROMIS PF short form 10a version 2.0 will be used in this study with a 7-day recall period. The items from the questionnaire are presented in Appendix 8.4. This PRO assessment consists of 10 questions and was constructed with a focus on representing the range of the trait and the content of the item bank, as well as mapping the questions in the instrument to qualitative evidence of the physical function concepts important to patients. A total sum score will be computed using all 10 items. A T-score and standard error of the T-score associated with the total score will be assigned based on the short form conversion table accompanying the scale and found in Appendix 8.4. A higher PROMIS T-score represents more of the concept being measured. For positively-worded concepts like physical function, a T-score of 60 is one SD better than average, and a participant with a T-score of 40 is one SD worse than the average (PROMIS, s.f.).

To supplement the PROMIS PF short form 10a, 3 additional questions representing other elements of physical function found to be important to patients were selected from the PROMIS Physical Function, Upper Extremity, and Ability to Participate item banks.

- Additional item 1: "Are you able to bend or twist your back",

- Additional item 2: "Are you able to reach into a high cupboard",
- Additional item 3: "I have trouble doing my regular daily work around the house".

A total score for the PROMIS-PF 10a with these three additional items has been supported by further psychometric evaluation. Therefore, a PROMIS PF13 score will be derived as a sum score of all 13 items, provided that there are no missing items.

Due to limitations in available translations in some countries, the additional 3 questions were not available at all sites. As such, this analysis only applies to those participants with available data at baseline including PROMIS PF short for 10a plus the 3 additional questions.

2.2.5. Patient Global Impression of Severity (PGIS)

The PGIS is a single-item scale that evaluates the participant's perception of the overall severity of their desmoid related symptoms over the past week on a 4-point scale ranging from "none" to "severe.". The PGIS has a 7-day recall period. The scale is presented in Appendix 8.5.

2.2.6. Patient Global Impression of Change (PGIC)

The PGIC is a single-item scale that evaluates the participant's perception of the change in their overall status since the start of the study treatment on a 7-point scale ranging from "very much better" to "very much worse". The PGIC has a 7-day recall period. The scale is presented in Appendix 8.6.

3. SUBJECT POPULATION

3.1. Population Definitions

The Intent-to-Treat (ITT) Population will be evaluated and used for presentation and analysis of the PRO data. The ITT Population will consist of all participants who are enrolled and randomized to study treatment (nirogacestat or placebo). Participants will be analyzed according to the treatment to which they were randomized and the strata to which they have been assigned. Participants who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

4. GENERAL STATISTICAL METHODS

4.1. General Methods

Continuous variables will be described by the number of participants, mean, median, standard deviation, minimum, and maximum. Categorical variables will be described by the number and percentage of participants within each category (with a category for missing data). Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. Additional conventions for presentation of study data are laid out in the main body of the NIR-DT-301 SAP and will be applied for the PRO analyses as appropriate.

Formal statistical hypothesis testing on the PRO-related secondary endpoints listed in section 2.1.3, for the purpose of New Drug Application (NDA), will be conducted at the 1-sided, 0.025 level of significance.

Specific details on analysis of selected PRO measures are laid out in Section 5. All additional PRO measures, as well as all data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed as described in an exploratory PRO statistical analysis plan and reported separately.

4.2. Baseline Definitions

For all PRO analyses unless specified, baseline for the double-blind phase will be defined as the most recent measurement prior to the first administration of study drug.

For weekly summary scores of the GODDESS and the BPI-SF, the baseline score will be set as the weekly average of the Baseline period (e.g., study days -7 through -1) if there are 4 or more days of assessments during that Baseline period. If there are less than 4 days of assessments during Baseline period, the baseline weekly score will be set to weekly average of the Screening visits' assessments, provided that there are 4 or more days of assessments during that period. Otherwise, it will be set as missing.

Baseline assessments of PGIC do not exist, as PGIC assessments are post-baseline only.

4.3. Adjustments for Covariates

In general, the stratification factor (as reported in randomization) will be included in the analysis of all PRO endpoints. In addition, longitudinal change from baseline models will account for the baseline scores.

4.4. Multiple Comparisons/Multiplicity

Multiplicity will be controlled via hierarchical testing method for the primary and secondary endpoints as defined in the main study SAP.

4.5. Subgroups

The longitudinal analysis of change from baseline in PRO endpoints and the time to pain response will be examined in selected subgroups as listed in Table 3.

Table 3 List of subgroups

Subgroup Name	**Subgroup Levels**
Primary tumor location as reported in randomization	Intra-abdominal
	Extra-abdominal
Baseline worst pain score	Uncontrolled (API > 4)
	Controlled (API ≤ 4)
Tumor focality	Multi-Focal Disease
	Single Tumor
Desmoid tumor treatment status	Treatment naïve, measurably progressing DT/AF that is deemed not amenable to surgery
	Recurrent, measurably progressing DT/AF following at least one line of therapy
	Refractory, measurably progressing DT/AF following at least one line of therapy
Sex	Male
	Female
Race	White
	Non-White
Geographic region	North America Sites
	Rest of World Sites
Age group	First age quartile
	Second age quartile
	Third age quartile
	Fourth age quartile
Ethnicity	Hispanic or Latino
	Not Hispanic or Latino

4.6. Withdrawals, Dropouts, Loss to Follow-up

Subjects who are withdrawn or discontinue from the study will not be replaced.

4.7. Missing, Unused, and Spurious Data

In case of missing items, the scale and total scores will be calculated as indicated in the scoring manual for the PRO instrument for the existing instruments. For GODDESS all items for a given total or domain score should be present in order to create the total or domain score.

Weekly scores (GODDESS and BPI-SF) will be calculated only if there are 4 or more days of assessments with non-missing data within the respective week.

It is anticipated that the great majority of missing data in this study will have a monotone pattern, meaning that once a participant has missing data at one visit, data will be missing at all subsequent visits. There may be some small amount of intermittent (non-monotone) missing data (when participant skips intermediate visits but returns for evaluations at subsequent visits).

Missing PRO data will be assumed to be missing at random (MAR) in general and will be analyzed using mixed model repeated measures (MMRM) analysis when appropriate. To address the possibility that missing data may not be MAR, sensitivity analysis with pattern mixture model (PMM) will be conducted.

4.8. Visit Windows

In line with the clinical SAP, no windowing conventions will be applied for the analysis of the PRO data. All data will be tabulated per the evaluation visit as recorded on the eCRF. In the case of multiple observations at a specific visit, the first observation will be used.

5. STUDY ANALYSES

5.1. Participant Disposition

The participant disposition by treatment arm for all PRO assessment timepoints in the double-blind phase will be provided:

- The number of participants with PRO assessment expected
- The number and % of participants with PRO assessment not expected due to progression
- The number and % of participants with PRO assessment not expected due to death
- The number and % of participants with PRO assessment not expected due to other reasons

The participant disposition by treatment arm per timepoint will also be provided graphically using bar charts.

A participant is expected to complete the PRO assessment as long as he/she is still alive and have not discontinued the study.

5.2. PRO Completion

PRO completion for all instruments will be examined at each timepoint in the double blind phase. Specifically, the following will be examined:

- Unadjusted completion rate at each timepoint will be calculated as the number of participants meeting at least the minimum requirements for scoring of each instrument divided by the number of participants in the ITT population.
- Adjusted completion rate at each timepoint will be calculated among participants who are expected to have PRO assessments.

For the adjusted completion rate described above, the following will be provided:

- The number and % of participants with all questions completed
- The number and % of participants meeting at least the minimum requirements for scoring of the instrument (see section 2.2
- The number and % of participants with at least one question completed (for multi-item instruments)

The completion rates (both adjusted and unadjusted) by treatment arm per timepoint will also be provided graphically: This will be displayed using grouped bar charts with visit on the x-axis and percent completion on the y-axis. Groups will be defined by treatment arm.

5.3. Exploration of Missing Data

Tabular summaries for the percentage of participants by the reason for discontinuation of study treatment, as well as for withdrawal from the study, are provided in the clinical SAP and will not be repeated herein.

The number of participants with missing PRO data will be summarized by treatment arm and timepoint (all scheduled timepoints in the double blind and OLE phases). For this analysis, the frequency and percentage of:

- Informative missingness, versus
- Non-informative missingness

The denominator will be the number of participants in the ITT.

This will be tabulated over time by treatment arm for each PRO endpoint. Informative missingness will be based on discontinuation due to an adverse event or due to lack of efficacy.

A comprehensive evaluation of missing data may warrant a modification to the planned analysis Any such modification will be detailed in the CSR.

5.4. Descriptive Analyses

Descriptive statistics for the observed scores as well as change from baseline scores for all the scores resulting from the instruments described in Section 2.2 except PGIS and PGIC will be provided for the ITT population by treatment arm at each timepoint in the double blind. Graphical representation will be also provided for the observed scores, e.g., box and whisker plots will be presented by treatment arm at each timepoint. Number and percentage of participants with each response value for PGIS and PGIC will be prestend by treatment arm at each timepoint.

A cumulative distribution function (CDF) plot showing a continuous plot of the change from baseline during the study, with change scores presented on the x-axis and the cumulative percent of participants experiencing that change on the y-axis, will be presented by treatment arm at all post-baseline timepoints up to and including Cycle 10. The cumulative distribution plot will be produced for the following PRO scores:

- DTSS scores: Total Symptom Score (weekly summary), Total Symptom Score – 5 Items (weekly summary), Pain Domain Score (weekly summary)
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API
- EORTC QLQ-C30: GHS/QoL, PF, RF and PA
- PROMIS: PF10a (sum score) and PF13 (sum score).

In addition, the number and proportion of participants by pain severity at baseline will be reported by treatment arms. Pain severity at baseline will be defined using the API score at baseline and classified as follows:

- Controlled pain at baseline: is API ≤ 4
- Uncontrolled pain at baseline: if API >4.

5.5. Longitudinal Analysis of Change from Baseline

Change from baseline during the double-blind phase in PRO scores will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach (Brown & Prescott, 2006) (MMRM – Mixed Model Repeated Measures) in a primary analysis and a PMM (O'Kelly & Ratitch, 2014) in a sensitivity analysis. The PMM will be used to assess the robustness of the MMRM estimate with regard to missing data, when the MAR assumption is replaced by assumptions that are likely to be relatively less favorable to the experimental treatment.

The longitudinal analysis of change from baseline will include only the on-treatment assessments (thus excluding the unscheduled, EOT and follow-up visits).

5.5.1. Mixed Model Repeated Measures – Main Analysis

The primary objective of this analysis is to examine the treatment difference at Cycle 10. Data from all PRO assessments at all scheduled timepoints will be reported, although analysis will be limited to timepoints at which at least 10 participants have non-missing data in both treatment arms through Cycle 10 (i.e, Cycle 11 on will not be included in the model) .

The response variable will be the change from baseline to each PRO assessment. The model will include the treatment arm and timepoint as fixed-effect categorical factors, the baseline PRO score and stratification factor (primary tumor location: intra-abdominal vs extra-abdominal) as fixed effects covariates, and the baseline x time and treatment x time interactions. Both main effects and the interaction terms will remain in the model, regardless of significance. The model will present least squares (LS) mean estimates, standard errors, 2-sided 95% CIs, and 1-sided p-values for mean changes from baseline to each visit.

A plot of the LS means accompanied by the 2-sided 95% CI will be produced for each PRO measure by treatment arm.

The analysis will be conducted using PROC MIXED in SAS. The model will assume unstructured covariance among the within-participant repeated measurements. If the algorithm does not converge, a heterogeneous Toeplitz (the TOEPH option in SAS PROC MIXED) will be tried first and then heterogenious autoregressive (ARH)(1) as a covariance structure to achieve convergence. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The analysis will be performed on the ITT population. Separate models will be considered for each of the following PRO score:

- DTSS scores: Total Symptom Score, Total Symptom Score – 5 Items, Pain Domain Score

- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API
- EORTC QLQ-C30: GHS/QoL, PF, RF and PA
- PROMIS: PF10a (sum score) and PF13 (sum score).

For the subgroup examinations, a separate model will be considered for each subgroup listed in Section 4.5. The model will include the treatment arm, and timepoint as fixed-effect categorical factors, the baseline PRO score, stratification factor (primary tumor location: intra-abdominal vs extra-abdominal, except for the stratification factor subgroup) and the subgroup as fixed effect covariates, and the baseline x time, treatment x time and treatment x subgroup interactions. The same hierarchy will be used to chose a covariance structure. Subgroup analyses will be run only for variables resulting in subgroups of at least 10 participants in each treatment arm. The following will be presented: least squares (LS) mean estimates for the overall treatment effect (across all timepoints), standard errors, 2-sided 95% CIs, and 1-sided p-values for mean changes from baseline to each visit, as well as the p-value for the treatment by subgroup interaction.

5.5.2. Pattern Mixture Model – Sensitivity Analysis

The MMRM assumes that the missing observations are MAR. To address the possibility of the data being missing not at random (MNAR) (e.g., non-ignorable missing data), a sensitivity analysis using a PMM with sequential modelling with multiple imputation and delta-adjustment will be used. Change from baseline to Cycle 10 in PRO scale will be analyzed using a pattern-mixture model using control-based approach by means of sequential modelling with multiple imputation as described by O'Kelly (O'Kelly & Ratitch, 2014). The results from this analysis will be used to judge the validity of the MAR assumption. Similar conclusions from MMRM and PMM would suggest that the results are not overly dependent on the assumptions of the primary analysis with regard to the missing data.

We distinguish between monotone and non-monotone missing values. Non-monotone missing values are values missing intermittently, where a participant may miss some PRO assessments but has PRO assessments for the same score later on. Monotone missing values are such that once a value is missing for a given score, no subsequent values for this score are available. Any given participant may have a combination of non-monotone and monotone missing values.

Non-monotone missing values are assumed to be MAR and will be multiply imputed using a Markov Chain Monte Carlo (MCMC) method of Proc MI in SAS. The imputation model will include the following:

- Treatment arms (nirogacestat or placebo)
- Stratification factors (primary tumor location:intra-abdominal vs extra-abdominal)
- Age (continuous)
- Gender (male or female)

- Geographic region (North America vs the rest of world)
- Desmoid Tumor Treatment Status (treatment naïve, recurrent or refractory)
- Any prior treatment (Yes vs No).

Non-monotone missing data will be imputed first, followed by the imputation of monotone missing data.

To impute monotone missing values, we define patterns depending on reason and timing of missingness as follows:

- **Pattern 1**: missing values before or at Cycle 10 due to participant's death;
- **Pattern 2**: missing values before or at Cycle 10 due to adverse events (AEs) or due to progression (clinical or radiographic);
- **Pattern 3**: missing values before or at Cycle 10 with missingness that does not satisfy conditions of patterns 1 to 2.

The patterns are mutually disjointed, i.e., each participant with monotone missing data belongs only to one pattern.

The following assumptions will be made for the missing data in each pattern:

For **pattern 1**, the worst score (e.g., 10 for DTSS Total Symptom Score) will be assigned as a penalty for unobservable values up Cycle 10 after participant's death. This will be applied to both treatment arms.

For **pattern 2**, control-based approach will be used for the nirogacestat arm. For the placebo arm, multiple imputation under MAR assumption will be used.

For **pattern 3**, data will be assumed to be MAR in both treatment arms.

The imputation of monotone missing data will be done sequentially for each scheduled PRO assessment visit, k=k1,…,K (where K corresponds to Cycle 10) as follows:

a) Impute monotone missing data in pattern 1 at visit k as the worst possible score for the imputed PRO score.

b) For the pattern 3 and for pattern 2 placebo participants only, impute the monotone missing values at visit k using an MAR-based multiple imputation regression model (PROC MI option MONOTONE REG) including the effects for baseline covariates as listed for the imputation model of non-monotone missing data above and PRO values at each schedule assessment time point up to (k-1).

c) For the pattern 2 nirogacestat participants only, impute the monotone missing values at visit k using multiple imputation regression model including the effects for baseline covariates as listed for the imputation model of non-monotone missing data above and PRO

values at each schedule assessment time point up to (k-1); at this step we will include all participants from the nirogacestat arm with missing at visit k, plus participants from the placebo arm with visit k observed. We omit participants from the nirogacestat arm with outcomes observed at vist k. Multiple imputation will now estimate regression parameters for visit k using data from the placebo arm only. The imputed data for vist k for a participant from the nirogacestat arm will look similar to the imputed data for a similar participant from the placebo arm.

The above steps (a)-(c) are performed for each visit k, before proceeding with the imputations of the next visit (k+1).

A total of 50 multiply-imputed datasets will be created for each PRO. The random number generator seed for the imputation of non-monotone missing values using MCMC will be 5414, and the random seed for imputation of monotone missing values will be 5414+k, for k=1, 2, … for each sequential visit with monotone missing data. For monotone missing imputation, the specified seed will be used for the first dataset. Data will be sorted so that the 1st dataset for each instrument is imputed, followed by the second dataset for each instrument, etc. Instruments will be ordered in the following manner:

- BPI-SF: API
- DTIS scores: Physical Functioning Domain Score
- DTSS scores: Total Symptom Score, Total Symptom Score – 5 Items, Pain Domain Score
- EORTC QLQ-C30: GHS/QoL, PF, RF and PA
- PROMIS: PF10a (sum score) and PF13 (sum score).

The MMRM modeling with the identical setup as described above in Section 5.5.1 will be performed, i.e., at each timepoint and also overall across all timepoints giving each visit equal weight, for each imputed dataset.

The SAS MIAnalyze procedure will be used to combine the results of these analyses for the imputations. For a more detailed description of the implementation MNAR imputation, see Ratitch B and O'Kelly M (O'Kelly & Ratitch, 2014).

The treatment differences will be estimated from the final model with LS-means differences and using the REML method. The degrees of freedom will be estimated with the Kenward-Roger approximation. The LS mean treatment difference, 2-sided 95% CI, and 1-sided p-value will be presented. A plot of the LS means accompanied by the 2-sided 95% CI will be produced by treatment and at each timepoint.

The analysis will be performed on the ITT population. Separate models will be considered for each of the following PRO scores:

- DTSS scores: Total Symptom Score, Total Symptom Score – 5 Items
- DTIS scores: Physical Functioning Domain Score

- BPI-SF: API
- EORTC QLQ-C30: GHS/QoL, PF and RF.

5.6. Responder Analysis

To understand meaningful changes experienced by participants at Cycle 10 (during the double-blind phase only), the frequency of responders vs. non-responders on the selected PRO measures will be reported and compared between the two arms. These change groups will be defined using either established (e.g.- literature based) thresholds where they exist, or empirically-derived thresholds for the newly developed instrument or when no literature values were observed (see Table 4). The responder analysis will be performed for the following measures:

- DTSS scores: Total Symptom Score, Pain Domain Score
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API.

For the GODDESS, as part of the psychometric analysis performed by IQVIA, clinically meaningful thresholds for improvement were also derived and will be used to define the responders and non-responders as described in Table 4 below.

Cut-off values of 30% or greater, or 2-point or greater change in numerical rating BPI-SF scores, have been proposed in the literature to detect clinically important improvements in cancer-related breakthrough pain and chronic pain states [(Farrar, et al., 2000) (Dworkin , et al., 2008)]. For this study, the value of 2 points will be used for API.

Table 4 Visit Responses for PRO Measures Based on Clinically Meaningful Thresholds

Instrument / Score	Primary threshold	Sensitivity 1 threshold	Sensitivity 2 threshold	Visit Response
GODDESS				
DTSS scores				
Total Symptom Score	CFB ≤ -1.4	CFB ≤ -1.0	CFB ≤ -1.7	Responder
	CFB > -1.4	CFB > -1.0	CFB > -1.7	Non-responder
Pain Domain Score	CFB ≤ -1.9	CFB ≤ -1.7	CFB ≤ -2.4	Responder
	CFB > -1.9	CFB > -1.7	CFB > -2.4	Non-responder
DTIS scores				
Physical Functioning Domain Score	CFB ≤ -0.8	CFB ≤ -0.6	CFB ≤ -1.0	Responder
	CFB > -0.8	CFB > -0.6	CFB > -1.0	Non-responder

CFB=change from baseline

The proportion of participants with improvement at Cycle 10 in PRO scores (e.g., responders) will be compared between the nirogacestat and placebo arms using using Cochran–Mantel–Haenszel test (CMH) test stratified by primary tumor location (intra-abdominal or extra-abdominal). Missing data at Cycle 10 will be imputed under the missing not at random

assumption. Specifically, multiple imputation under the MNAR assumption as described in Section 5.5.2 will be performed first to impute the continuous PRO scores. Next, a visit response (responder vs non-responder) at Cycle 10 will be derived as described above for each PRO score for each of the 50 datasets generated in the imputation procedure. The analysis will include only those patients with a baseline score ≥ threshold value used to define improvement (see Table 4 for GODDESS, for BPI-SF a value of 2 will be used).

Each of the multiply-imputed data sets with the response visit status at Cycle 10 will be analysed using the CMH test adjusted by primary tumor location (intra-abdominal or extra-abdominal) used. Statistical inference obtained from all imputed data will be combined using Rubin's rule (Ratitch, et al., 2013). The odds ratio will be log-transformed and the Wilson-Hilferty transformation will be applied to the CMH statistitic prior to combining all results with PROC MIANALYZE. The visit response by treatment arm (average, minimum and maximum percent responder), odds ratio (OR) as well as the corresponding 2-sided 95% CI will be provided along with the 1-sided p-values.

A descriptive analysis will also be performed. The number and proportion of participants who are responders vs. non-responders (as defined in the Table 4 above) will be summarized at each post-baseline timepoint (the double-blind phase only) by treatment arm. The proportions will be derived in two ways. In the first analysis, the denominator will be the number of participants with non-missing data at specific cycle. In a second analysis, the denominator will be the number of participants in the ITT population for whom a PRO is expected (i.e., including participants with missing data) at specific cycle. Participants with missing data at specific cycle will be considered non-responders in this second analysis. The proportion of participants who are responders vs non-responders in the second analysis described above will be presented graphically using bar charts.

In addition, for the DTSS Total Symptom Score, Pain Domain Score, and BPI-SF API, a symptom improvement rate will be defined as the number and proportion of participants who are responders at two or more consecutive timepoints during the double-blind period (see Table 4). This analysis will be performed only among those particpants with uncontrolled pain at baseline (e.g., with a baseline API ≥4) and will use all the available datapoints during double-blind phase. The improvement rate will be compared using a logistic regression stratified by primary tumor location (intra-abdominal or extra-abdominal). Additional covariates, such as age and gender, will also be examined and included as appropriate. The results of the analysis will be presented in terms of an OR together with its associated 2-sided 95% CI and 1-sided p-value.

5.7. Time to Event Analysis

Time to event analyses will include all PRO assessments during the double-blind phase (thus any unscheduled and EOT visits) and will be performed separately for the following PRO scores:

- DTSS scores: Total Symptom Score, Pain Domain Score
- DTIS scores: Physical Functioning Domain Score
- BPI-SF: API.

The following time to event endpoints will be defined:

- Time to first DT symptom improvement (using DTSS Total Symptom)
- Time to first control of pain symptoms (using BPI-SF API)
- Time to pain response (using BPI-SF API, DTSS Pain Domain Score)
- Time to first improvement in functioning (using DTIS: Physical Functioning Domain Score)

Time to first DT symptom improvement will be defined as the duration of time from the date of randomization to the date of the first time reduction of at least a X points in DT symptoms using the DTSS Total Symptom Score (X is the threshold value which is provided in Table 4) as compared to the baseline score. The primary threshold as well as both sensitivity thresholds will be used. Participants without observed symptom improvement at the time of analysis will be censored at the date of last available PRO assessment (i.e., date of the last non-missing value) on or before the analysis data cutoff date. Participants who were randomized but with no baseline or whose baseline scores do not allow for further improvement will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

Time to first control of pain symptoms will be defined as the time from randomization to first time the BPI-SF API score is ≤ 4. The analysis will include only those participants whose BPI-SF API baseline scores are > 4. Participants without observed control of pain symptoms at the time of analysis will be censored at the date of last pain assessment on or before the analysis data cutoff date. Participants who were randomized but with no baseline score will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

Time to pain response will be defined using the BPI-SF API and DTSS Pain Domain Score as follows: time to pain response is defined as the time from randomization to first occurence of pain response (using 2 points for BPI-SF API and the values in Table 4 for DTSS Pain Domain Score). Participants without observed pain response at the time of analysis will be censored at the date of last pain assessment on or before the analysis data cutoff date. Participants who were randomized but with no baseline or whose baseline scores do not allow for further reduction in pain will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

Time to first improvement in functioning will be defined using the DTIS Physical Functioning Domain Score as follows: time to clinically meaningful improvement is defined as the time from randomization to first occurrence of improvement (e.g., response, see Table 4). Participants without observed improvement at the time of analysis will be censored at the date of last PRO assessment on or before the analysis data cutoff date. Participants who were randomized but with no baseline or whose baseline scores do not allow for further improvement will be censored on the date of randomization. Participants with a baseline score but no post-baseline assessments will be censored at the baseline assessment date.

For all time to event analyses, the time to event will be analyzed in months and will be presented

by treatment arm. Kaplan-Meier curves will be presented. The hazard ratio (HR) and the 95% CI will be estimated using a Cox proportional hazards model controlling for stratification factor (primary tumor location [intra-abdominal or extra-abdominal]). Additional covariates, such as age or gender, will also be examined and included as appropriate.

A 1-sided stratified log-rank test on the time to event will be performed using SAS PROC LIFETEST with method=PL option (Kaplan-Meier estimates, also known as the product-limit estimates). The HR with 2-sided 95% CI will be estimated from the stratified Cox proportional hazards model using SAS PHREG procedure with ties=EXACT option in the model. In this analysis, the baseline hazard function will be allowed to vary across strata; i.e., the MODEL statement will include the treatment arm variable as the only covariate and the STRATA statement will include the prespecified variable. The assumption of proportionality will be tested by producing plots of complementary log-log (event times) versus log(time).

Kaplan-Meier plots of the survival distribution function will be presented and include the number of participants at risk over time by treatment arm.

The time to pain response will also be examined in selected subgroups (see Section 4.5). For the subgroup examinations, separate unstratified Cox models will be employed for each subgroup listed in Section 4.5. The model will include the treatment arm, the subgroup and treatment x subgroup interaction. Subgroup analyses will be run only if at least 10 events occurred in one of the subgroups across treatment groups. The following will be presented for each subgroup: the number of participants, events and censored cases, the median time to event and the corresponding 2-sided 95% CI , HR with 2-sided 95% CI and the 1-sided p-value corresponding to the stratified log-rank test, as well as the 2-sided p-value obtained from the unstratified Cox for the treatment by subgroup interaction.

6. CHANGES TO PLANNED ANALYSES

As of this date, there have been one notable change between the protocol-defined statistical analyses of the PRO data and those presented in this statistical analysis plan:

"Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks" has been moved from secondary to exploratory endpoint, due to duplications to other PROs instruments.

7. REFERENCES

Brown, H. & Prescott, R., 2006. *Applied Mixed Models in Medicine.* s.l.:John Wiley and Sons Ltd.

Dworkin , R., Turk, D. & Wyrwich, K., 2008. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Pain,* Volume 9, pp. 105-21.

Farrar, J. et al., 2000. Defining the clinically important difference in pain outcome measures. *Pain,* Volume 88, pp. 287-94.

Fayers, P. et al., 2001. EORTC QLQ-C30 Scoring Manual (3rd ed.). *EORTC.*

O'Kelly, M. & Ratitch, B., 2014. *Clinical Trials with Missing Data: A Guide for Practitioners..* s.l.:John Wiley & Sons Ltd.

PROMIS, n.d. Physical functioning: A brief guide to the PROMIS Physical Function instruments. *Patient-Reported Outcomes Measurement Information System (PROMIS).*

Ratitch, B., Lipkovich, I. & O'Kelly, M., 2013. *Combining Analysis Results from Multiply Imputed Categorical Data.* [Online]
Available at: https://www.lexjansen.com/pharmasug/2013/SP/PharmaSUG-2013-SP03.pdf
[Accessed 17 December 2021].

8. APPENDICES

8.1. The GOunder/DTRF DEsmoid Symptom/Impact Scale (GODDESS)

8.1.1. Items of Desmoid Tumor Impact Scale (DTIS)

Item #	Question	Scale	Range
1	During the past 7 days How often have you had difficulty moving (for example twisting or bending) near your tumor?	5	None - All the time
2	How often have you had difficulty with reaching up, such as reaching shelves that were above your head?	5	None - All the time
3	How often have you had trouble falling asleep?	5	None - All the time
4	How often have you had difficulty getting comfortable in bed?	5	None - All the time
5	How often have you had trouble staying asleep at night?	5	None - All the time
6	How often have you had difficulty doing vigorous activities (such as running, lifting heavy objects, or participating in strenuous sports)?	5	None - All the time
7	How often have you had difficulty doing moderate activities (such as pushing a vacuum cleaner, playing with children, or taking a long walk)?	5	None - All the time
8	How often have you accomplished less than you would like when doing work or other regular daily activities?	5	None - All the time
9	How often have you avoided people because of the way you feel about your appearance?	5	None - All the time
10	What was your worst difficulty with reaching up, such as reaching shelves that were above your head?	11	0 - 10
11	Have you been dissatisfied about your appearance?	11	0 - 10
12	How much fear of future diagnostic tests did you have?	11	0 - 10
13	How much fear of recurrence / growth of your desmoid tumor(s) did you have?	11	0 - 10
14	How much hopelessness did you have?	11	0 - 10
15	How much anger did you have?	11	0 - 10
16	How much anxiety did you have?	11	0 - 10
17	How much frustration did you have?	11	0 - 10

8.1.2. Items of Desmoid Tumor Symptom Scale (DTSS)

Item #	Question	Scale	Range	Note
	During the past 24 hours			
1	How bad was your worst feeling of pain?	11	0 - 10	
2	How bad was your worst feeling of dull pain?	11	0 - 10	
3	How bad was your worst feeling of shooting pain?	11	0 - 10	
4	How bad was your worst feeling of fatigue?	11	0 - 10	
5	What was your worst swelling around your tumor(s)?	11	0 - 10	
6	What was your worst muscle weakness around your tumor(s)?	11	0 - 10	
7	At its worst, how difficult was moving (for example twisting or bending) near your tumor(s)?	11	0 - 10	
8	Please indicate the location(s) of your desmoid tumor(s). Select all that apply.			Gate Q for Q9 - Q11
9	How bad was your worst feeling of abdominal pain?	11	0 - 10	If Abdominal Wall in Q8
10	How bad was your worst feeling of nausea?	11	0 - 10	If Abdominal Wall in Q8
11	How bad was your worst feeling of fullness after beginning to eat?	11	0 - 10	If Abdominal Wall in Q8

8.2. BPI Short Form

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

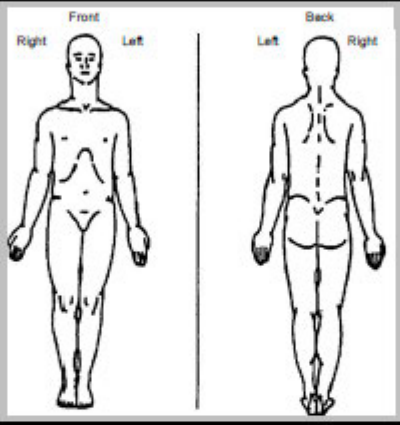
Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ___/___/____ Time: _____
Name: _____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

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8.3. EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Scoring the EORTC QLQ-C30 version 3.0

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS-1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

8.4. PROMIS

8.4.1. PROMIS PF Short Form 10a

PROMIS® Item Bank v2.0 – Physical Function – Short Form 10a

Physical Function – Short Form 10a

Please respond to each question or statement by marking one box per row.

		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36r1	Does your health now limit you in walking more than a mile (1.6 km)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Cannot do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA10r1	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA56	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45r1	Are you able to sit on and get up from the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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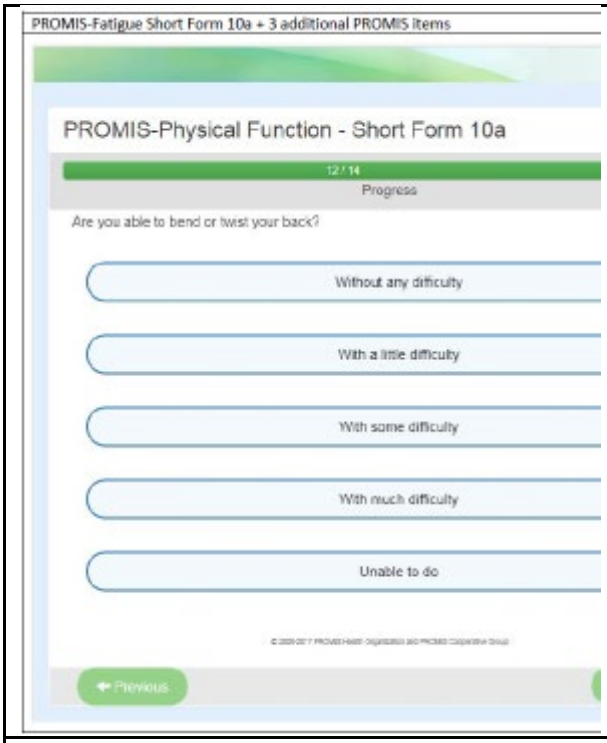
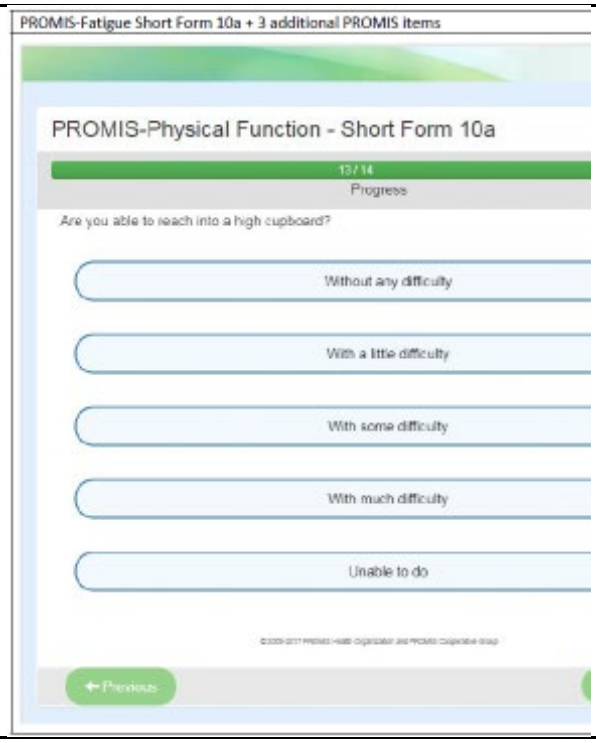
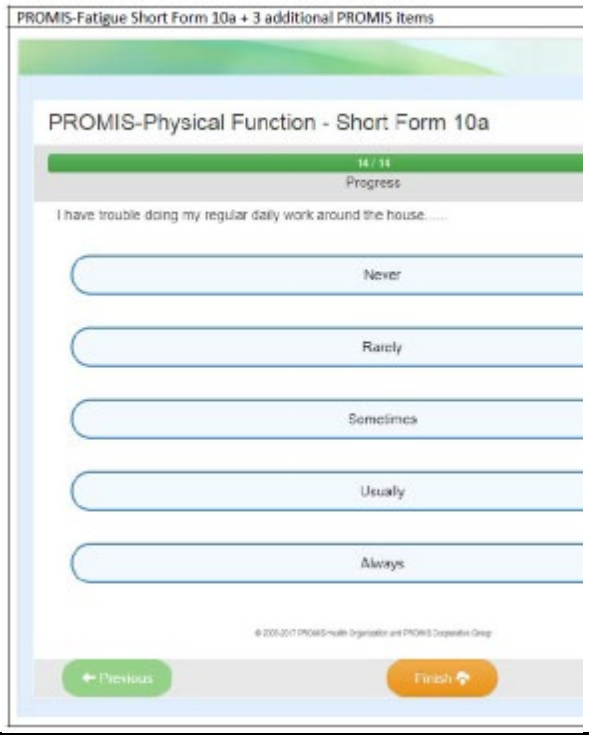
8.4.2. PROMIS PF Short Form 10a Look-Up Table

Adult v2.0 – Physical Function 10a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
10	13.5	3.6
11	16.6	2.8
12	18.3	2.7
13	19.7	2.5
14	20.9	2.4
15	22.1	2.3
16	23.1	2.2
17	24.1	2.2
18	25.0	2.1
19	26.0	2.0
20	26.9	2.0
21	27.7	1.9
22	28.6	1.9
23	29.4	1.9
24	30.2	1.8
25	31.0	1.8
26	31.8	1.8
27	32.5	1.8
28	33.3	1.7
29	34.0	1.7
30	34.8	1.7
31	35.5	1.7
32	36.3	1.7
33	37.0	1.7
34	37.8	1.7
35	38.5	1.8
36	39.3	1.8
37	40.1	1.8
38	40.9	1.9
39	41.7	1.9
40	42.6	1.9
41	43.5	2.0
42	44.4	2.1
43	45.5	2.1
44	46.6	2.3
45	47.9	2.5
46	49.4	2.8
47	51.2	3.2
48	53.4	3.6
49	55.8	3.9
50	61.9	5.9
*SE = Standard Error on T-score metric		

8.4.3. 3 Additional Items from PROMIS Item Banks







8.5. PGIS

Please choose the response below that best describes the severity of your desmoid related symptoms over the past week.

□ None

□ Mild

□ Moderate

□ Severe

8.6. PGIC

Please choose the response below that best describes the overall change in your general state of health since you started taking your study medication.

□ Very much Better

□ Moderately Better

□ A Litter Better

□ No Change

□ A Little Worse

□ Moderately Worse

□ Very much Worse