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

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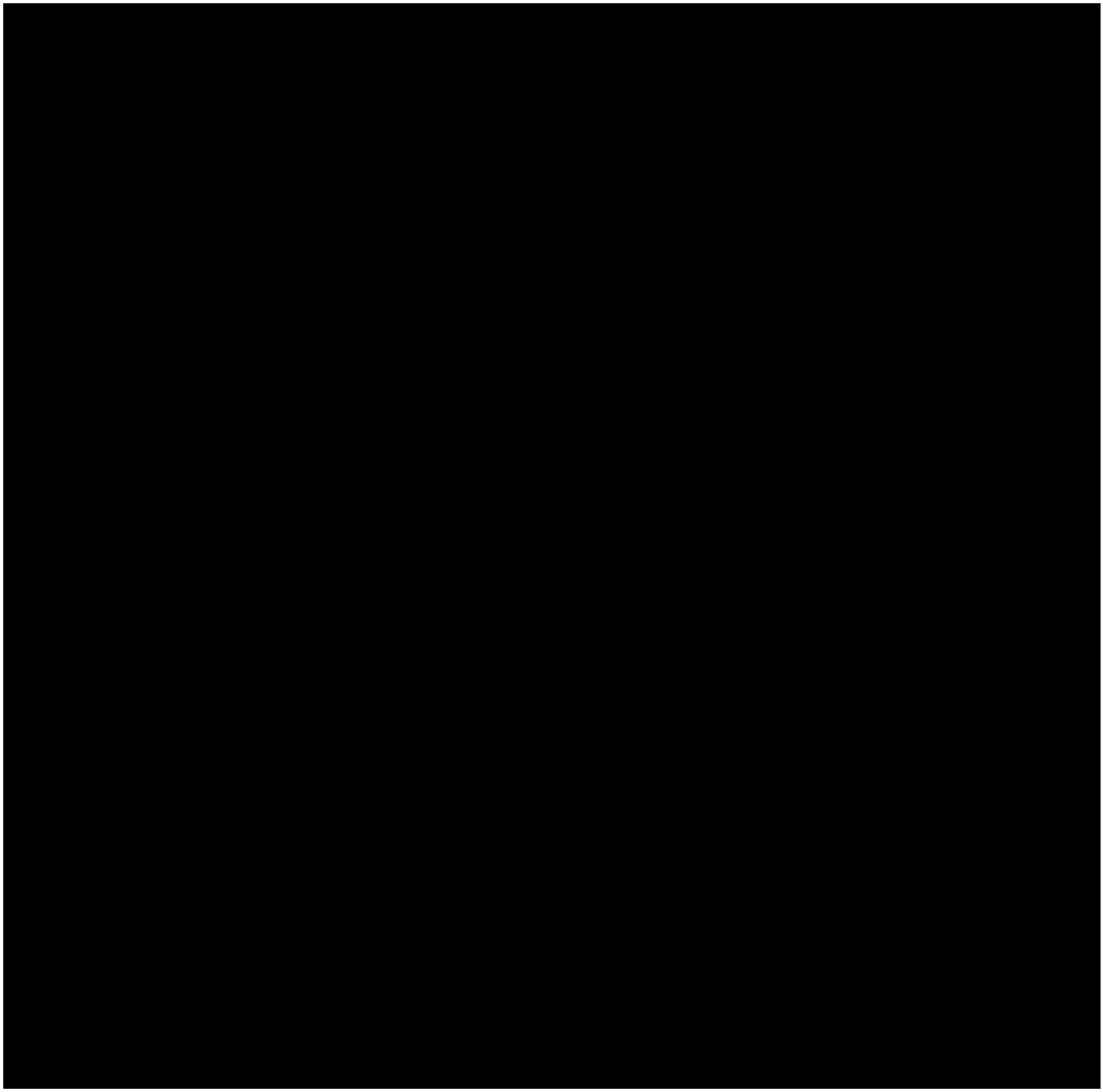

Protocol Amendment Summary of Changes Table

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

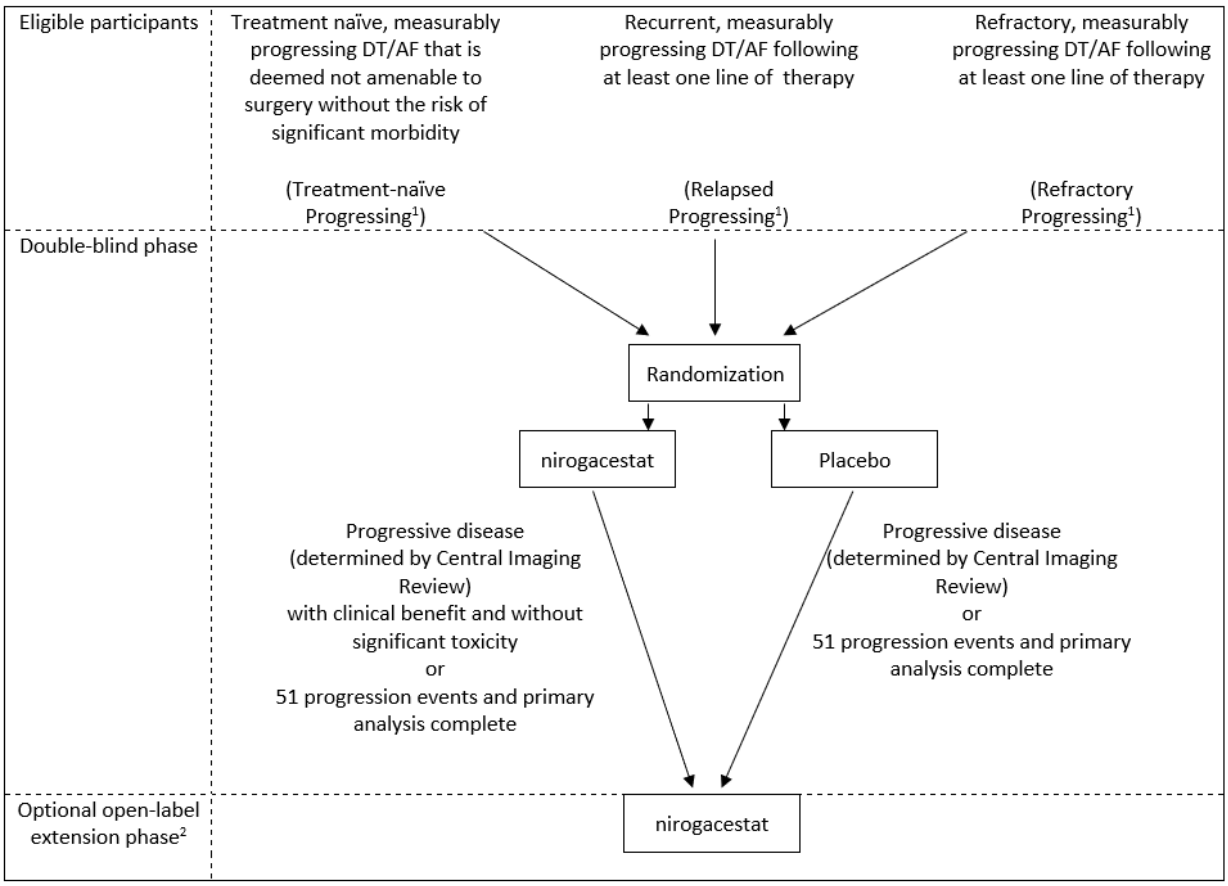
will remain in the double-blind phase until death, disease progression, they prematurely discontinue study treatment for any reason, the study is stopped by the sponsor for any reason, or the required number of PFS events have been observed and the primary PFS analysis has been completed (based on current 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:

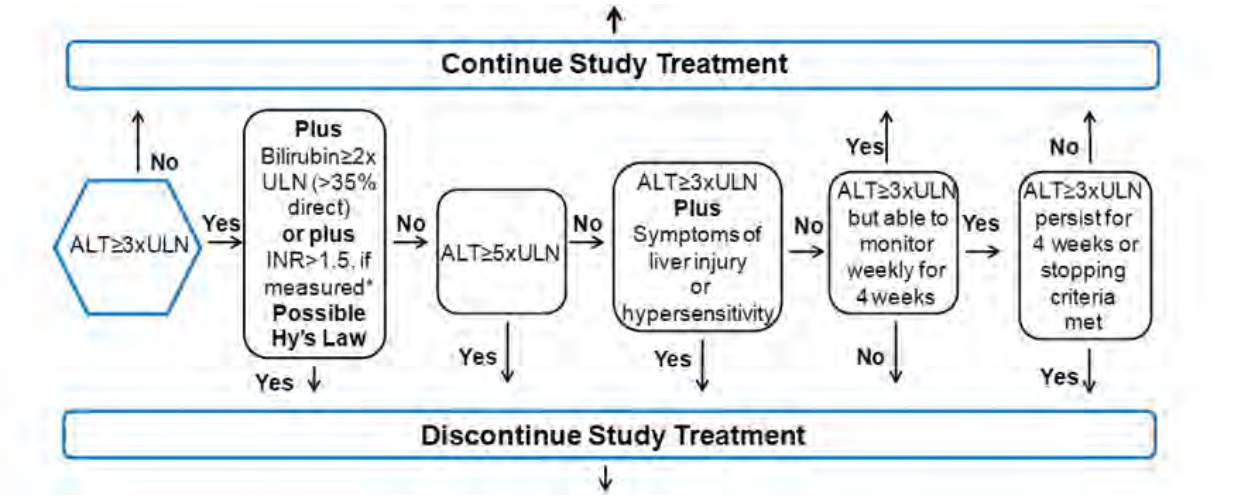
- Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1) in the double-blind phase and the participant does **not** enter the OLE phase;
- Central Imaging Review determines that a participant has radiographic progressive disease (using RECIST v1.1);
- 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.

Tumor biopsy reminders:

- 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:
  ○ MCV
  ○ MCH
• % Reticulocytes
• WBCC with Differential[1]:
  ○ neutrophils
  ○ lymphocytes
  ○ monocytes
  ○ eosinophils
  ○ 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
			  ○ HBsAg
			• HCV
			  ○ 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 Meeting 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.

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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

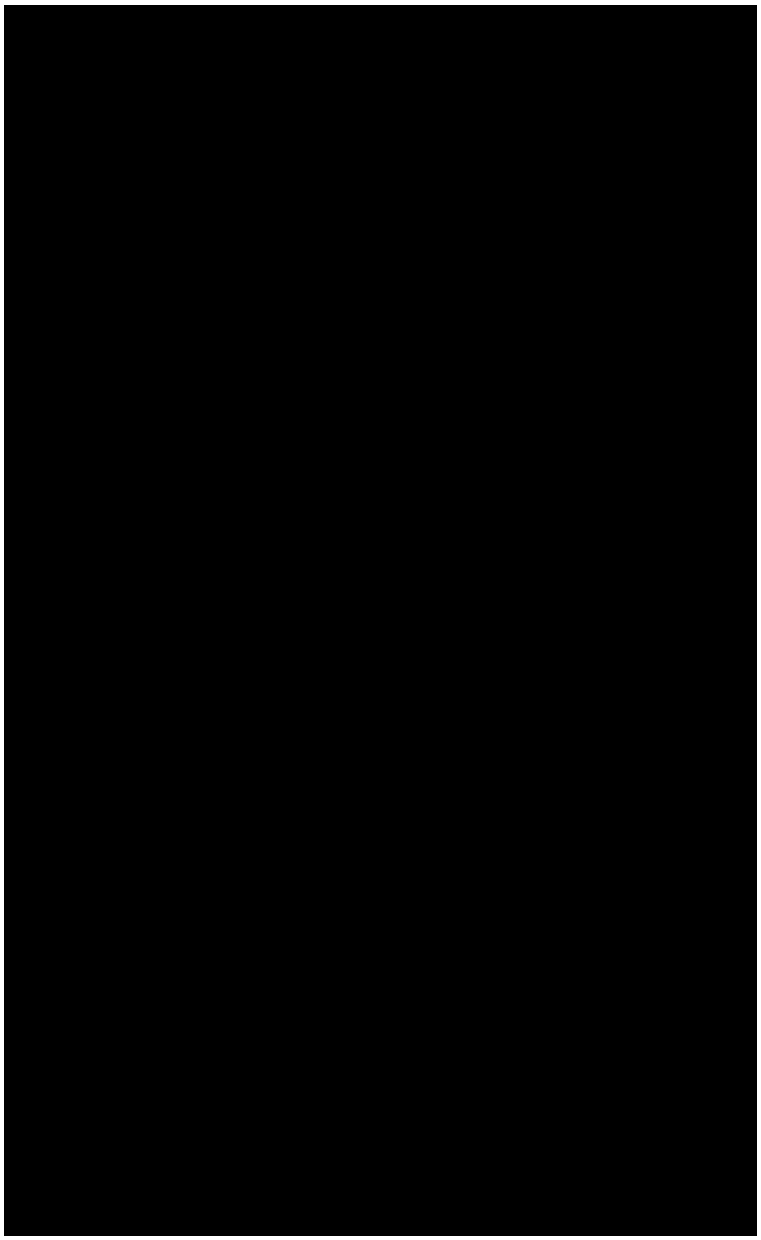
Abbreviation	Definition
GGT	Gamma-glutamyl transferase;
GODDESS	GOunder/DTRF DEsmoid Symptom/Impact Scale
GS	Gamma-secretase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
Hes1	Hairy and enhancer of split-1
HGB	Hemoglobin
HIV	Human immunodeficiency virus
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
100 Washington Blvd
Stamford, CT 06902
United States
Telephone: 212-421-8012
Fax: 646-609-8816



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