STATISTICAL ANALYSIS PLAN

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

Protocol Number:	NIR-DT-301
Protocol Version and Date:	Amendment 5: 09 February 2021 Amendment 4: 07 July 2020 (not released to sites) Amendment 3: 27 January 2020 Amendment 2: 14 October 2019 Amendment 1: 09 July 2019 Original: 03 August 2018
Name of Test Drug:	Nirogacestat
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Placebo-Controlled
Sponsor:	SpringWorks Therapeutics 100 Washington Blvd. Stamford, CT 06902 United States
Sponsor Representative:	[redacted] Sponsor Biostatistician
Analysis Plan Date:	12 May 2022
Analysis Plan Version:	Final Version 2.0

Author:

[redacted]
PharPoint Research, Inc

Date

Sponsor Signatory

[redacted]
SpringWorks Therapeutics, Inc

Date

[redacted]
SpringWorks Therapeutics, Inc

Date

TABLE OF CONTENTS

Section **Page**

TABLE OF CONTENTS 3
LIST OF TABLES 7
1. INFORMATION FROM THE STUDY PROTOCOL 10
1.1. Introduction and Objectives 10
1.1.1. Introduction 10
1.1.2. Study Objectives 11
1.2. Study Design 12
1.2.1. Synopsis of Study Design 12
1.2.2. Randomization Methodology 12
1.2.3. Stopping Rules and Unblinding 13
1.2.4. Study Procedures 13
1.2.5. Efficacy and Safety Endpoints 27
1.2.5.1. Primary Efficacy Endpoint 27
1.2.5.2. Secondary Efficacy Endpoints 27
1.2.5.3. Exploratory Endpoints 28
1.2.5.4. Safety Parameters 28
2. SUBJECT POPULATION 29
2.1. Population Definitions 29
2.2. Protocol Deviations 29
2.3. Impacts from COVID-19 30
3. GENERAL STATISTICAL METHODS 31
3.1. Sample Size Justification 31
3.2. General Methods 31
3.3. Computing Environment 32
3.4. Baseline Definitions 32
3.5. Methods of Pooling Data 32
3.6. Adjustments for Covariates 33
3.7. Multiple Comparisons/Multiplicity 33
3.8. Subgroups 33
3.9. Withdrawals, Dropouts, Loss to Follow-up 35

Section **Page**

3.10. Missing, Unused, and Spurious Data....35
3.11. Visit Windows....36
4. STUDY ANALYSES....37
4.1. Disposition....37
4.2. Demographics, Baseline Characteristics, and Medical History....37
4.2.1. Prior Therapy....38
4.3. Efficacy Evaluations....38
4.3.1. Primary Efficacy Evaluation....38
4.3.1.1. Analysis of Progression Free Survival....40
4.3.1.2. Sensitivity Analyses of PFS....40
4.3.1.3. Subgroup Analysis....41
4.3.2. Secondary Efficacy Evaluations....41
4.3.2.1. Objective Response Rate (ORR)....41
4.3.2.2. Analysis of PRO Assessment data....42
4.3.3. Exploratory and Other Supportive Efficacy Analyses....43

4.3.3.1. Best Overall Response (BOR) 43
4.3.3.2. Disease Control Rate (DCR) 44
4.3.3.3. Time to Tumor Progression (TTP) 44
4.3.3.4. PFS at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period 44
4.3.3.5. DOR at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period 44
4.3.3.6. Time to Response 44
4.3.3.7. Change in Tumor Volume Assessed by MRI 44
4.3.3.8. Change in Sum of Largest Diameter of Tumor Assessed by RECIST 45
4.3.3.9. Tumor Response by Exposure 45
4.3.3.10. Change in Tumor Volume by Tumor Response 46
4.3.3.11. Change in Symptoms by Exposure and Change in Tumor Size/Volume 46
4.3.3.12. PFS by Mutation Status in APC and CTNNB1 Genes 47
4.3.3.13. Other Prognostic Factors 47
4.3.3.14. Change in Expression of Notch Genes 47
4.3.3.15. Change in MRI T2 intensity 47
4.3.3.16. Change in MRI T2 intensity by Tumor Response 47
4.3.3.17. DT Specific Comorbidity 47
4.3.3.18. Local vs Central RECIST v1.1 Readings 48
4.4. Safety Analyses 48
4.4.1. Study Drug Exposure and Compliance 48
4.4.2. Adverse Events 49
4.4.2.1. Selected Treatment Emergent Adverse Events 50
4.4.2.2. Adverse Events of Special Interest 52
4.4.2.3. DT Specific Comorbidity 52
4.4.3. Clinical Safety Laboratory Assessments 52
4.4.4. Physical Examinations and Eastern Cooperative Oncology Group Performance Status 54
4.4.5. Electrocardiogram 54
4.4.6. Vital Signs 55

Section **Page**

4.4.7. Concomitant Medications and Procedures....55
4.5. Pharmacokinetic and Pharmacodynamic Analyses....55
5. CHANGES TO PLANNED ANALYSES....56
6. REFERENCES....57
7. APPENDICES....58
7.1. Handling of Missing/Partial Dates for AEs....58
7.2. Handling of Missing/Partial Dates for Concomitant Therapies/Medications....58
7.3. Handling of Missing Dates for Disease History and Prior Therapies....59
7.4. Consolidated Medication Coding....59
7.5. Preferred Terms for Adverse Event Analyses....61
7.5.1. Ovarian Dysfunction (OD)....61
7.5.2. Rash, Hidradenitis, Hair Follicle AEs....62
7.5.2.1. Rash....62
7.5.2.2. Hidradenitis....64
7.5.2.3. Hair Follicle AEs....64
8. CLINICAL STUDY REPORT APPENDICES....66
8.1. Statistical Tables, Figures and Listings to be Generated....66

LIST OF TABLES

Table 1. Schedule of Assessments (SoA) – Double-Blind Phase 14
Table 2. Schedule of Assessments (SoA) – Open-Label Extension Phase 21
Table 3. Subgroup for Efficacy Analyses 34
Table 4. Subgroup Definition for Safety Analyses 35
Table 5. Primary PFS Censoring Methodology 39
Table 6. BOR Determination Table 43
Table 7. Eastern Cooperative Oncology Group Performance Status Grades 54
Table 8. Broad Summary of Preferred Terms to Describe Ovarian Dysfunction in WOCBP 61
Table 9. Broad Summary of Preferred Terms to Describe Rash 63
Table 10. Broad Summary of Preferred Terms to Describe Rash 64
Table 11. Broad Summary of Preferred Terms to Hair Follicle Adverse Events 65

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
APC	Adenomatous polyposis coli
BOR	Best Overall Response
BPI	Brief Pain Inventory
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double-blind
DOR	Duration of response
DT/AF	Desmoid Tumors/Aggressive Fibromatosis
DTIS	Desmoid Tumor Symptom Scale
DTSS	Desmoid Tumor Impact Scale
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
FAP	Familial adenomatous polyposis
FUP	Follow-up
GODDESS	GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale
HR	Hazard ratio
IRT	Interactive response technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
OD	Ovarian dysfunction
OLE	Open-label extension
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic

Abbreviation	Definition
PP	Per-Protocol
PR	Partial response
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System Physical Function
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	International System of Units
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This document is the statistical analysis plan (SAP) for NIR-DT-301, a Phase 3, randomized, double-blind, placebo-controlled study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF). It is based on Protocol Amendment 5, dated 09 February 2021. The safety and efficacy for the double-blind phase of NIR-DT-301 will be discussed in two parts:

1. The main body of the SAP (Main SAP) will detail the statistical analyses to be conducted using clinical data for the primary analysis data cut after approximately 51 events have occurred and a final double-blind phase analysis after last-participant last visit (LPLV) for the double-blind phase of the study and
2. A patient-reported outcome (PRO) Addendum for analysis of PRO data.

As with the study's Main SAP, the PRO Addendum will be finalized before the unblinding of the clinical database once the target number of events have been observed. Analysis of pharmacokinetic (PK) data from samples collected during the study will be described in a separate PK SAP that documents the integrated PK analyses (including data from early phase studies) for nirogacestat. An End of open-label extension (OLE) SAP will be developed for the OLE phase data.

The primary analysis of safety, efficacy, and tolerability is planned after approximately 51 events have occurred in the double-blind phase of the study (primary analysis data cut). A clinical study report will be developed using the primary analysis data cut. A final analysis of the double-blind phase of the study will be performed after the last participant last visit has occurred for the double-blind phase of the study; this final analysis will inform safety and nominal p-values will be presented for efficacy endpoints, but no interpretation will be made on these results. Unless otherwise specified, the analysis covered by this document will include only clinical data collected during the double-blind (DB) phase of the study. The various SAP components for study NIR-DT-301 are summarized below:

SAP Component	Focus	SAP Completion Date
Main SAP	Analysis of safety and efficacy based on clinical data collected during the DB phase of the study including the primary analysis after approximately 51 events have occurred and end of double-blind phase analysis after (LPLV)	Prior to unblinding
PRO Addendum	Analysis of PRO data based on data collected during the DB phase of the study	Prior to unblinding
PK SAP	Integrated analysis of nirogacestat PK data, including PK samples collected in NIR-DT-301	Prior to unblinding
End of OLE SAP	Analyses for long-term outcomes based on clinical and PRO data collected during the DB and OLE phases of the study	Prior to the End of the OLE phase

1.1.2. Study Objectives

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The primary objective of this study is:

- To determine the efficacy (as defined by progression-free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF

The secondary objectives of this study are:

- To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of AEs
- To determine the Objective Response Rate (complete response [CR] + partial response [PR]) of nirogacestat in participants with progressing DT/AF
    - To describe the duration of response (DOR) and duration of stable disease (DOSD) when data is available
- To evaluate desmoid tumor symptoms and impacts using the following patient-reported outcomes (PROs):
    - GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS)
    - Brief Pain Inventory (BPI) short form
    - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30

The exploratory objectives of this study are:

- To compare tumor volume changes measured by magnetic resonance imaging (MRI) in participants with progressing DT/AF
- To evaluate desmoid tumor symptoms and impacts using the following PROs:
    - Patient Global Impression of Severity (PGIS)
    - Patient Global Impression of Change (PGIC)
- To perform genotyping for germline and somatic mutation in adenomatous polyposis coli (APC) and β-catenin genes (CTNNB1)
- To assess modulation of the Notch pathway by evaluating NOTCH response genes in tumor biopsies at screening and disease progression or end of treatment (EOT)

- To assess MRI T2 hyperintensity at baseline and post-drug administration
- To inform development of a population pharmacokinetic (PK) model of nirogacestat
- To perform exposure-response analysis using a final population PK/PD (PopPK/PD) model
- To evaluate the effect of nirogacestat on clinical events related to disease specific desmoid tumor co-morbidity

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. 142 eligible participants were randomized to study treatment (nirogacestat or placebo) in a 1:1 ratio. Randomization was stratified by primary tumor location (intra-abdominal or extra-abdominal).

This study will consist of 2 phases: the double-blind phase and the optional OLE phase. Refer to the schedule of activities (SoA Table 1 and Table 2) for details on assessments and timing of study visits.

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

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

1.2.2. Randomization Methodology

Randomization will be stratified based on the following tumor locations:

1. Intra-abdominal (include mesentery and pelvis)

   OR

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

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

1.2.3. Stopping Rules and Unblinding

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

If central imaging review determines that a participant has radiographic progressive disease (using Response Evaluation Criteria In Solid Tumors [RECIST] v1.1) during the double-blind phase of the study, the site will be notified by the central imaging core laboratory. The participant will then return for the EOT visit which will unblind the participant and participant will have the option to enter OLE phase, if eligible. All EOT assessments and all ongoing adverse events (AEs) / serious AEs (SAEs) must (1) be assessed for causality by the investigator or qualified designee in a blinded manner and (2) recorded in the electronic case report form (eCRF) prior to the unblinding of the study treatment allocation.

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

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

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, are provided in Table 1 (for double-blind phase) and Table 2 (for OLE phase). Please note that references to specific sections and table numbers in the schedules (and the associated table footnotes) are referring to sections and tables within the study protocol.

Table 1. Schedule of Assessments (SoA) – Double-Blind Phase

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

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

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

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

1. **Screening visit:** Assessments may occur up to 28 days prior to first dose of study treatment with a minimum screening period of 14 days to allow for participant completion of the screening and baseline PRO assessments (refer to Protocol Table 8 for PRO administration schedule). An extension to the screening period may be permitted on a case-by-case basis following discussion between the investigator and the medical monitor/sponsor. The reason(s) for the extension must be clearly documented.

2. **Informed consent process:** Includes participant signing the ICF and must be conducted prior to any study related procedures being performed. The date the participant signs the ICF will be Day 1 of the screening period. Refer to Protocol Section 10.1.3 for more detail on the ICF process.

3. **Baseline visit:** Assessments may be performed over a 48-hour period. All baseline assessments are to be conducted prior to first dose of study treatment except for the following assessments: post-dose 12-Lead ECGs and post-dose blood draws for pharmacokinetic (serial PK) sampling.

4. **ECOG performance status:** At baseline, assessment must be done prior to first dose of study treatment. Refer to Protocol Section 10.7 for ECOG scale.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

    20a. Screening visit scans:

- MRI and CT scans obtained during the screening visit will serve as the participant's baseline scan for the study (CT scan only required if it is the chosen modality for RECIST v1.1 tumor measurement). Scans should be submitted to central imaging core laboratory as early in the screening period as possible to confirm scan quality is acceptable for analysis prior to randomization.
- Standard of care scan(s) acquired prior to the participant signing ICF may be used as the participant's screening visit scan(s) if obtained within 28 days of the first dose of study treatment and the quality of the scans are acceptable for analysis (as determined by the central imaging core laboratory). These scans will then be collected, stored, and documented as the screening visit scan(s). No other pre-enrollment images will be collected for central reading.

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

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

21. **Randomization:** Participants will not be randomized to study treatment using IRT until all I/E criteria (Protocol Sections 5.1 and 5.2) have been confirmed and all pre-randomization baseline study assessments have been completed.

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

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

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

25. **AEs/SAEs:** Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Refer to Protocol Section 8.3 for more detail. Females reporting AEs/AESIs/SAEs of primary ovarian insufficiency (POI) and/or amenorrhea will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).

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

27. **EOT visit:** EOT visit should be conducted prior to study treatment discontinuation to avoid a gap in study treatment for participants entering the OLE phase. All EOT assessments must be conducted prior to unblinding (if applicable refer to Protocol Section 6.3.2.1).

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

If the participant discontinues study treatment for any reason other than progressive disease (as determined by Central Imaging Review using RECIST v1.1), they will be encouraged to return to the site as soon as possible to complete the EOT visit assessments prior to study treatment discontinuation or as close as possible to the last dose of study treatment.

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

Table 2. Schedule of Assessments (SoA) – Open-Label Extension Phase

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

OLE Phase **Cycle Number**	**Cycle 1[5]** *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2[5]**	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Cycle Day	**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Blood for male hormone levels[11]	X[11a]					X	X	X	X
Urinalysis[12]	*Same as double-blind EOT*				X	X	X	X	X
Urine pregnancy test (WOCBP only)[13]	*Same as double-blind EOT*			X	X	*(Monthly)[13a]*		X	X
Patient-Reported Outcomes (PROs)[14]									
GODDESS (symptom scale)					*(Monthly assessment, refer to Protocol Table 9)*		*(Quarterly assessment, refer to Protocol Table 9)*		*(Refer to Protocol Table 9)*
BPI short form									
PROMIS PF short form 10a plus 3 additional items from PROMIS item banks									
GODDESS (impact scale)									
EORTC QLQ-C30									
PGIS									
PGIC									
Imaging and RECIST									
CT or MRI scan for tumor measurement (using RECIST v1.1)[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	

OLE Phase **Cycle Number**	**Cycle 1[5]** *(Applicable only to participants previously randomized to placebo in the double-blind phase)*				**Cycle 2[5]**	**Cycles 4, 7, 10**	**Cycle 13 & Every 3 Cycles**	**EOT[20]**	**Follow-Up[21]**
Cycle Day	**Day 1 Baseline[3]**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 1**		
Visit Week *Calendar Day* *(Visit Window)*	**Week 1** *Day 1* *Same day as, or up to 24 hours after, double-blind EOT*	**Week 2** *Day 8* *(± 2 days)*	**Week 3** *Day 15* *(± 2 days)*	**Week 4** *Day 22* *(± 2 days)*	**Week 8** *Day 56* *(± 2 days)*	**Weeks 13, 25, 37** *Days 85, 169, 253* *(± 7 days)*	**Week 49 & On** *Day 337 & On* *(± 7 days)*	*See footnote 20 for visit window*	*30 days after last dose (+ 7 days)*
Local RECIST v1.1 read[15]	*Same as double-blind EOT*					X	X[15a] *(Cycle 13 and then every 6 cycles)*	X[15b]	
Enrollment and Study Treatment									
Enrollment/first dose of open-label study treatment[4]	X								
Study treatment dispensing[16]	X					X	X		
Study treatment administration/diary[17]	←	—	—	—	—	—	→		
Study treatment accountability						X	X	X	
Ongoing Monitoring									
Monthly wellness checks[18]	←	—	—	—	—	—	→		
ConMed review	←	—	—	—	—	—	—	—	→
AE/SAE review[19]									

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

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

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

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

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

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

   9b. At Cycle 1 Day 8 visit, triplicate ECGs are required 1-hour (±10 minutes) post-dose. Applicable to participants who were previously randomized to receive placebo in the double-blind study phase only.
10. **PK sampling:** Refer to Protocol Section 8.5 and central laboratory manual for sample processing details.

    10a. Serial PK: Only applicable to participants who were previously randomized to receive placebo in the double-blind study phase. PK samples should be collected on OLE Cycle 1 Day 1 at the following timepoints: pre-dose and 0.25-, 0.5-, 1-, 1.5-, 2- and 3-hours post-dose. All efforts will be

made to obtain within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing. Out of window PK draws will not be captured as deviations if the exact time of the sample collection is noted on the source documents and eCRF.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1.2.5. Efficacy and Safety Endpoints

1.2.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, which is defined as the time (in months) from randomization until the date of assessment of progression or death by any cause (whichever occurs first). Specifically,

$$\text{PFS} = (\text{Date of progression or death} - \text{Date of randomization} + 1) / 30.4375$$

Progression will be determined radiographically using RECIST v1.1 (Eisenhauer, 2009) or clinically as assessed by the investigator. Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF. Events of clinical progression will be adjudicated by an independent blinded central Endpoint Adjudication Committee (EAC) which will qualify events of clinical progression for inclusion in the PFS endpoint prior to study unblinding according to an EAC Review Charter.

Study participants who discontinue the study due to clinical progression and the progression does not qualify as determined by EAC will be censored at the time of last response assessment.

Participants who have not progressed or died will be censored based on the rules outlined in Table 5. Participants who do not have any response assessments will be censored at the date of randomization. Sensitivity analysis utilizing alternative censoring methods will be described in Section 4.3.1.2.

1.2.5.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Objective Response Rate (ORR), defined in Section 4.3.2.1
    - Duration of responses (in months) as supportive, descriptive analyses of ORR, defined in Section 4.3.2.1.1
- Change in PRO measures from baseline over time, as defined in Section 4.3.2.2 (as well as in the PRO Addendum):
    - GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale
    - Brief Pain Inventory (BPI) short form
    - European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-Core 30 (QLQ-C30)

1.2.5.3. Exploratory Endpoints

Exploratory efficacy endpoints include:

- Change in tumor volume from baseline as assessed by MRI volumetric
- Changes using the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC)
- Frequency and distribution of germline and somatic mutations in APC and CTNNB1 genes
- Change in expression pre- and post-dose on Notch pathway genes
- Percent change in MRI T2 intensity
- PK samples to increase precision of model parameters
- Exposure-response analysis using a final population PK/PD (PopPK/PD) model to determine relationship between exposure and primary, secondary and/or exploratory efficacy and safety endpoints
- The incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity which may include hospitalization as a result of small bowel obstruction, hospitalization due to desmoid tumor-related pain or surgery for desmoid tumor

1.2.5.4. Safety Parameters

The safety endpoints are evaluated by means of study treatment-related AE reports, physical examinations, and laboratory safety evaluations.

AEs will be monitored continuously via safety laboratory assessments, ECGs, vital signs, and physical examinations. Clinically significant changes in physical examination findings, laboratory assessments, and vital signs will be reported as AEs.

2. SUBJECT POPULATION

2.1. Population Definitions

The following participant populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: The ITT Population will consist of all participants who are enrolled and randomized to study treatment (nirogacestat or placebo). Participants will be analyzed according to the treatment they were randomized to and the strata to which they have been assigned. Participants who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.
- Per-Protocol (PP) Population: The PP Population will consist of those participants who received study drug and have no major protocol deviations. Major protocol deviations are defined in Section 2.2. and will be determined prior to unblinding. Participants will be analyzed according to the study treatment actually received. In addition to major protocol deviations, those participants who meet the following criteria may also be excluded from this population:
  - Do not have confirmed diagnosis of DT/AF per Inclusion Criterion #2
  - Mis-randomization
  - Permanent discontinuation due to non-compliance with study drug
- Safety Population: The Safety Population will consist of all participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

The ITT population is the primary analysis population for the efficacy analyses. The PP population will be used for supportive analyses as needed. The Safety population will be the primary analysis population for the safety analyses.

2.2. Protocol Deviations

Protocol deviations are reviewed in accordance with the Protocol Deviation Plan prior to unblinding of the study results and the conduct of the primary statistical analyses. A data listing of all reportable PDs including a description of the deviation will be generated. Major protocol deviations are defined as reportable deviations that may impact the accuracy and or reliability of the efficacy data. Major protocol deviations impacting the efficacy analysis will be identified prior to conducting the primary statistical analysis.

The number and percentage of participants with reportable protocol deviations not due to COVID-19 and reportable protocol deviations due to COVID-19 will be summarized overall and by category of deviation, including inclusion/exclusion criteria, investigational product, restricted concomitant medication use, study-required imaging, withdrawal criteria, safety reporting, informed consent, study procedures, and study required ePRO assessments.

2.3. Impacts from COVID-19

This study was conducted during the global SARS-Cov-2 pandemic. The impact of COVID-19 was mitigated based on the evolving EMA and FDA COVID-19 guidelines [European Medicines Agency 2021; US Food and Drug Administration 2020].

A summary table and listing of all patients impacted by COVID-19 and how their participation in the study was altered, including missed visits, missed assessments and other deviations from protocol procedures due to COVID-19 will be provided.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The study sample size is based on the primary PFS endpoint. A total of 51 events will provide 90% power and a 1-sided type 1 error rate of 0.025 (1-side hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat group is 20 months and 8 months in the placebo group (corresponding to a hazard ratio of 0.4 relative to placebo). Assuming a 10% dropout rate and a 20% spontaneous regression rate, 118 participants will be randomized in a 1:1 ratio to observe the required number of events.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day associated with double-blind phase treatment start (Rel Day). Pre-treatment and on-treatment study days in double-blind phase represented as Rel Day are numbered relative to the day of the first dose of study medication in double-blind phase which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc. If applicable, placebo subjects that have entered open-label phase will have a second relative study day derived associated with starting active treatment within open-label phase (OLE Day). On-treatment study days in open-label phase for placebo subjects represented as OLE Day are numbered relative to the day of first dose of open-label treatment which is designated as OLE Day 1 and will follow same rules as Rel Day.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of participants, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

Formal statistical hypothesis testing on the primary endpoint, for the purpose of New Drug Application (NDA), will be conducted at the 1-sided, 0.025 level of significance. Type I errors for secondary endpoints will be controlled using a hierarchical testing procedure. Summary statistics and modeling results for secondary and exploratory endpoints will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

Data will be presented by participant and summarized by treatment.

Graphical displays will be provided where useful to aid in the interpretation of results.

In addition, the following data conventions will be applied:

- P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places
- P-values less than 0.001 will be presented as "<0.001;" P-values greater than 0.999 will be presented as ">0.999"
- CIs will be presented to 1 more decimal place than the raw data
- Weeks will be calculated as number of days divided by 7
- Months will be calculated as number of days divided by 30.4375
- Years will be calculated as number of days divided by 365.25
- Cycles as used in adverse event summaries are defined as every 28 days
- Day 1 will be considered as the first day of treatment in double-blind phase
- All tables, figures, and listings will include footers at the bottom of the page reflecting the path of the programs used to generate the tables, figures, and listings, and date and time of the generation of the output

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version March 2019 or later.

3.4. Baseline Definitions

For all analyses, baseline for the double-blind phase will be defined as the most recent measurement prior to or on the first administration of study drug. For the OLE phase, baseline will be defined as the most recent assessment prior to the first administration of nirogacestat. Therefore, for participants who are assigned to the placebo arm during the DB phase and who enter the OLE phase, this will result in a secondary baseline for OLE which will be defined as the most recent measurement prior to the first administration of active treatment.

3.5. Methods of Pooling Data

Data will be pooled across study sites.

3.6. Adjustments for Covariates

The stratified log-rank test and Cox proportional hazards model will include the randomization strata as a covariate (strata). In general, the stratification factor will be included in the analysis of the primary and secondary endpoints.

Analyses accounting for baseline demographics or disease characteristics may be conducted as part of supportive analyses. This includes each of the subgroup variables listed in Section 3.8 which will be considered for inclusion as covariates in the multivariable models where noted.

3.7. Multiple Comparisons/Multiplicity

Multiplicity will be controlled via hierarchical testing method for the primary and secondary endpoints in the order as listed in Section 4.3.

3.8. Subgroups

Select efficacy endpoints (PFS and Objective Response Rate [ORR]) will be examined in (tables and forest plots) the following subgroups:

Table 3. Subgroup for Efficacy Analyses

Stratification	
Stratification factor as reported in randomization	
Demographics	
Sex (Male vs Female)	Age (by quartile)
Race (White vs Non-White)	Ethnicity
Geographic region (North America vs the rest of world)	BMI (18.5 kg/m^2,18.5 - < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
Disease Characteristics	
Multi-focal disease vs single tumor	Baseline target lesion size by quartile
Baseline target lesion locations[1]	
Prior Treatment	
Any prior therapy (Yes vs No)	Number of prior lines of therapies (0, 1-3, 4+)
Prior systemic therapy (Yes vs No)	Prior surgical treatment (Yes vs No)
Prior radiation treatment (Yes vs No)	Previous exposure with sorafenib (Yes vs No)
Prior chemotherapy exposure (Yes vs No)	Prior tyrosine kinase inhibitor exposure (Yes vs No)
	Desmoid tumor treatment status[2]
Dose Modification	
Dosed per protocol vs reduction (Yes vs No)	Relative Dose Intensity (≤ 80% vs > 80%)
Genetic Mutation	
History of familial adenomatous polyposis (FAP)	Presence of any CTNNB1 mutation, somatic CTNNB1 mutation, or germline CTNNB1 mutation
Presence of any APC mutation, somatic APC mutation, or germline APC mutation	
Adverse Event	
Highest Reported FSH in women of childbearing potential (WOCBP) by range indicator (Low/Normal, High)	WOCBP with events of ovarian dysfunction (as defined by a narrow list of terms per Section 7.5.1) that have resolved versus those that have not resolved
Participants with AEs of Rash or Alopecia (as defined by all narrow terms in Section 7.5.2).	Participants with AEs of Diarrhea within the first 3 cycles

[1] Baseline target lesion location is based on actual target tumor location from the Electronic Database. Baseline target lesion locations: Intra-Abdominal (including mesentery and pelvis) and Extra-Abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations). If a participant has multiple target tumors that are located in both the intra and extra-abdominal location, the tumor will be classified as intra-abdominal.
[2] Desmoid tumor treatment status: 1) Treatment naïve, measurably progressing DT/AF, 2) Recurrent, measurably progressing DT/AF following at least one line of therapy, and 3) Refractory, measurably progressing DT/AF following at least one line of therapy

TEAE and treatment-related AEs will be examined in the following subgroups:

Table 4. Subgroup Definition for Safety Analyses

Stratification	
Stratification factor as reported in randomization	
Demographics	
Sex (Male vs Female)	Age (by quartile)
Race (White vs Non-White)	Ethnicity
Geographic Region (North America vs the rest of world)	BMI (18.5 kg/m^2, 18.5 - < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
Disease Characteristics	
Multi-focal disease vs single tumor	Baseline target lesion size by quartile
Baseline target lesion locations[1]	
Prior Treatment	
Any prior therapy (Yes vs No)	Number of prior lines of therapies (0, 1-3, vs 4+)
Prior systemic therapy (Yes vs No)	Prior surgical treatment (Yes vs No)
Prior radiation treatment (Yes vs No)	Previous exposure with sorafenib (Yes vs No)
Prior chemotherapy exposure (Yes vs No)	Prior tyrosine kinase inhibitor exposure (Yes vs No)
Desmoid tumor treatment status[2]	
Dose Modification	
Dosed per protocol vs reduction (Yes vs No)	Relative Dose Intensity (≤ 80% vs > 80%)
Genetic Mutation	
History of familial adenomatous polyposis (FAP)	Presence of any CTNNB1 mutation, somatic CTNNB1 mutation, or germline CTNNB1 mutation
Presence of any APC mutation, somatic APC mutation, or germline APC mutation	

[1] Baseline target lesion location is based on actual target tumor location from the Electronic Database. Baseline target lesion locations: Intra-Abdominal (including mesentery and pelvis) and Extra-Abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations). If a participant has multiple target tumors that are located in both the intra and extra-abdominal location, the tumor will be classified as intra-abdominal.
[2] Desmoid tumor treatment status: 1) Treatment naïve, measurably progressing DT/AF, 2) Recurrent, measurably progressing DT/AF following at least one line of therapy, and 3) Refractory, measurably progressing DT/AF following at least one line of therapy.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Participants who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR. Methods for handling incomplete PRO instruments will be performed according to their scoring manuals, if

available. The imputation of partial/missing dates for AEs, concomitant therapies/medications, and disease history/prior therapies are described in Section 7.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there is data from an unscheduled or additional visit that is inside the visit window, the data from the unscheduled or additional visit will be used in data summaries. In data listings, the relative day of all dates to first study dose will be presented.

4. STUDY ANALYSES

4.1. Disposition

The total number of participants who were screened (who have signed the informed consent), the number randomized, and the number in each study population will be summarized by treatment arm and overall. The number of randomized participants in each primary tumor location stratum will also be presented.

In addition, summaries will be presented for the number and percent of participants who:

- Discontinued treatment and reasons for treatment discontinuation in the double-blind phase
- Discontinued the study and reasons for study discontinuation
- Continued to the open label study
- Discontinued treatment and reasons for treatment discontinuation in the OLE phase
- Participants who discontinued double-blind treatment but chose to not enter OLE

All treatment and study discontinuation data will be listed. A by-participant data listing of inclusion and exclusion criteria not met will be presented.

4.2. Demographics, Baseline Characteristics, and Medical History

Demographics and baseline characteristics will be summarized for the ITT and Safety populations by treatment arm and overall. In addition, medical history (including overall medical history and any history of infertility) and disease characteristics will also be summarized for the safety and ITT populations.

Demographics will include univariate statistics for age at time of informed consent (years), baseline weight, baseline height, baseline body mass index (kg/m^2); and categorical summaries for sex, women of childbearing potential (yes / no) for females, menstrual history for females, infertility history for males and females, age, baseline ECOG, race, ethnicity, BMI group and geographic region. Menstrual history for females includes history of amenorrhea (yes / no) and menstrual irregularities (yes / no) collected on the eCRF page.

Disease characteristics to be summarized include time (in month) since date of diagnosis to randomization, presence of multi-focal disease versus single tumor, number of target tumors and target tumor location(s), desmoid tumor treatment status (treatment-naïve, recurrent or refractory disease), baseline target lesion size, family history of FAP, any mutation of APC or CTNNB1, somatic mutation status of APC and CTNNB1, germline mutation status of APC and CTNNB1 and total number of non-target tumors seen by central reviewers and location(s) of non-target tumors based on stratification factor and as reported in EDC.

Demographic and baseline data for each participant will be provided in data listings.

4.2.1. Prior Therapy

Prior therapies will be summarized by treatment arm and overall based on the ITT population. The variables will include any prior therapy (surgery, radiation, systemic) (yes / no), prior therapeutic surgery (yes / no) and resection margins, prior radiation therapy (yes / no), prior sorafenib exposure (yes / no), prior TKI exposure (yes/no) [defined as medications in the ATC classes of 'BCR-ABL TYROSINE KINASE INHIBITORS', "OTHER PROTEIN KINASE INHIBITORS'], prior systemic therapy (yes / no), type of prior systemic therapies, number of lines of prior systemic therapies and responses, and months from most recent prior systemic therapy to randomization. The total number of prior therapies will also be summarized by treatment arm and overall.

The duration to be summarized is defined as follows.

- Months from most recent prior systemic therapy to randomization will be calculated as (date of randomization – stop date of most recent systemic therapy) / (30.4375).

The imputation of partial/missing dates is described in Section 7.

Additionally, prior surgeries and systemic therapies will be presented in separate tables summarizing SOC (or ATC) and PT by treatment arm and overall. Prior radiotherapies will also be summarized by type by treatment arm and overall. Prior systemic therapies will be summarized using modified PT. PTs will be modified to be grouped as outlined in Appendix 7.4 to consolidate brand and generic medication names for the same active ingredient into a single line item to facilitate reporting of the same medication. Both the original and modified PTs will be included in the listings. If a participant experiences multiple surgeries or procedures under the same PT (or SOC/ATC), then the participant will be counted only once for that PT (or SOC/ATC).

All prior therapy data will be listed in participant data listings.

4.3. Efficacy Evaluations

The primary and secondary efficacy endpoints will be tested in the following order: PFS, objective response rate, disease symptoms, impact, and quality of life evaluations by PRO. If the null hypothesis is rejected at the specified significance level, the testing may proceed to the next endpoint, but if the null hypothesis is not rejected, all subsequent results will be considered descriptive only. All data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed and reported separately.

Efficacy analyses will be conducted using the ITT population.

4.3.1. Primary Efficacy Evaluation

The primary efficacy endpoint is PFS, where disease progression is determined by either independent, blinded central imaging review using RECIST v1.1 as described in Section 8.1.2 of the protocol, or clinically as assessed by an investigator whose assessment is qualified via independent blinded central clinical review as described in Section 8.1.2 of the protocol. The primary efficacy analysis will be performed after approximately 51 events have been observed.

PFS will be analyzed using a 1-sided stratified log-rank test to compare the distributions between nirogacestat and placebo at alpha level of 0.025. PFS data will be summarized with Kaplan-Meier methodology. Two sided 95% CIs for the median time-to-event in each study treatment arm and the hazard rate ratio will be computed.

PFS will be calculated from time of randomization to the earlier date of progression or death due to any cause. The progression date will be determined based on the date of scan for events that are verified by blinded independent central imaging review using RECIST v1.1. For qualified events of clinical progression, it will be the earliest date of onset or worsening of symptoms resulting in a global deterioration of health status.

In situations where study participants are discontinued early from the study by investigators for clinical progression but cannot be verified as qualified events, they will be considered as dropouts and will be censored for the primary analysis. Similarly, participants who do not progress or die will be censored at the date of the last valid computed tomography (CT)/MRI assessment.

Censoring rules for the primary analysis are outlined in Table 5.

Table 5. Primary PFS Censoring Methodology

Situation	Date of Censoring of Event	Outcome
No adequate disease status assessment	Date of randomization	Censored
No documented progression or death	Date of last adequate disease status assessment	Censored
Progression that has been verified by the central imaging review using RECIST v1.1 with ≤1 missing consecutive scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of progression	Event
Early discontinuation by study investigator due to clinical progression that has been verified as qualified event by the independent Event Adjudication Committee (EAC) for primary analysis	Earliest date of onset or worsening of symptoms resulting in a global deterioration of health status as documented by the date of clinical progression in the case report form	Event
Early discontinuation by study investigator due to clinical progression that do not meet the definition of a qualified event per protocol as judged by the EAC.	Date of last adequate disease status assessment	Censored
Death before progression being documented with ≤1 missing scheduled disease status assessment before death	Date of death	Event
New anticancer therapy or procedure started prior to documented radiographic or clinical progression	Date of last adequate disease status assessment before the new therapy	Censored

4.3.1.1. Analysis of Progression Free Survival

Kaplan-Meier curves will be presented, and HR and the 95% CI will be estimated using a Cox proportional hazards model controlling for stratification factor the participant is assigned to at randomization (primary tumor location - intra-abdominal vs extra-abdominal).

A stratified log-rank test on PFS will be performed using SAS PROC LIFETEST with method = PL option (Kaplan-Meier estimates, also known as the product-limit estimates). The hazard ratio with 2-sided 95% CI will be estimated from the stratified Cox proportional hazards model using SAS PHREG procedure with ties = EXACT option in the model. In this analysis, the baseline hazard function will be allowed to vary across strata, i.e., the MODEL statement will include treatment arm variable as the only covariate and the STRATA statement will include tumor location.

Number of participants with events, types of events (progression or death before progression), number of participants censored, number of participants for each reason of censoring, quartiles (i.e., the 25th, 50th (median), 75th percentile estimates), and 95% confidence intervals for PFS will be calculated from the product-limit method and presented by treatment arm. Kaplan-Meier plots of the survival distribution function will be presented and include the number of participants at risk over time by treatment arm. Additionally, a spider plot of percent change from baseline in tumor size over time will be presented. Time at which best overall response occurred (for participants with CR or PR) will be annotated as will when the participant is off treatment. A swimmer plot of duration of treatment will be produced where progression, first response, and death are noted.

4.3.1.2. Sensitivity Analyses of PFS

The following sensitivity analyses will be performed

a) Calculation of PFS using only events confirmed by central radiographic review per RECIST v1.1
b) Calculation of PFS including all PI-determined clinical progressions to assess the impact of the criteria used to determine qualified event adjudicated by EAC on the primary endpoint
c) Analysis using the PP set using the primary endpoint censoring rules
d) Using the date of the first missing assessment as the date of progression for participants who progressed radiographically right after 2 or more consecutively missed radiological assessments
e) Using local RECIST results of PI selected target tumor, instead of results from the central review, for the 15 participants whose scans are read prior to the implementation of Protocol Amendment 2 (which included the implementation of PI selection of target lesions for central review)
f) Additional sensitivity analyses using only subjects with centrally confirmed diagnosis of DT/AF

g) A sensitivity analysis using interval-censoring methodology for PFS will be performed. When the exact date of progression is not observed due to scheduled assessment, these progression events are considered interval censored. The right side of the interval will be the date of progression as defined in Table 5, and the left side of the interval will be the last adjudicated assessment for disease progression before the right side of the interval. If there is no adjudicated assessment before the date of progression, the left side of the interval will be the randomization date. Participants without a PFS qualified event will be right censored with the same censoring rules as specified in Table 5.

   A generalized stratified log-rank test stratified by the stratification factor will be performed for treatment comparison using SAS PROC ICLIFETEST (Guo, et al, 2014). This procedure will also be used to estimate the survival function for PFS with the EMICM method, which is a combination of the EM algorithm and iterative convex minorant algorithm. A multiple imputation method will be used to estimate the standard error of the survival function using SEED =138207.

In addition, to estimate the median PFS follow-up time at the time of analysis, a time-to censoring analysis will be performed by reversing the censoring indicator used in the primary PFS analysis, i.e., the censored becomes an event and the PFS event becomes censored.

4.3.1.3. Subgroup Analysis

Subgroup analyses of the primary efficacy will be performed on the ITT population using the subgroups specified in Section 3.8. If there are too few events (≤5) in a particular subgroup level, only descriptive summaries will be provided.

For each subgroup, HR and associated CIs will be calculated from a stratified Cox proportional hazards model. The stratification factor in the primary analysis will be used in the subgroup analyses when applicable. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI for the overall group. Summaries of the number and percentage of participants experiencing a PFS event for each subgroup will be provided along with the median PFS by treatment arm.

4.3.2. Secondary Efficacy Evaluations

Secondary endpoints are described in Section 1.2.5.1. Secondary efficacy analyses will be conducted using the ITT population unless otherwise specified. The hierarchy for testing secondary endpoints will follow the order of their appearance below.

4.3.2.1. Objective Response Rate (ORR)

ORR will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. Response used for the definition of ORR is defined as having a confirmed Best Overall Response (BOR) of CR or PR by RECIST v1.1 during the blinded portion of the study, where BOR is defined in Section 4.3.3.1. Summaries of ORR and the 2-sided 95% exact CI will be presented.

4.3.2.1.1. Duration of Response

Duration of Objective Response and duration of stable disease are supportive, descriptive analyses for ORR. Duration of Objective Response (DoOR) is defined as the duration in months from the time measurement criteria are met for CR or PR (whichever comes first) until the date of progression or death (whichever comes first). Duration of Stable Disease (DoSD) is defined as the duration in months from the start of treatment until the date of progression or death (whichever comes first).

Pending data availability, DoOR will be analyzed using the Kaplan-Meier method based on participants with a documented response (CR or PR) only. Estimates for the 25th percentile, 50th percentile (median), and 75th percentile for DoOR (as well as the range) will be presented by treatment arms. Similarly, DoSD will be analyzed on participants with CR, PR, or SD only. Kaplan-Meier plots for DoOR and DoSD will be provided, respectively. The censoring method will be the same as that for the primary endpoint (Section 4.3.1). Since the number of the participants available for analysis is random, no formal testing between the two treatment arms will be conducted for both DoOR and DoSD.

By-participant listings will be provided for DoOR and DoSD separately. DoOR listing will include number of completed cycles before first response, date of first response, date of progression or death if any, and DoOR. DoSD listing will include date of first study treatment, date of progression or death if any, and DoSD. Censored or event will be marked. Additionally, to evaluate efficacy compared to previous treatment, number of prior therapies will be added to the listings. Swimmer plots will be used to present duration of responses over time for each participant.

4.3.2.2. Analysis of PRO Assessment data

Due to the number of instruments used in the study and the complexity of the planned analyses, a PRO Addendum was created specifically to detail the PRO data analysis methods to be used. The endpoints and testing hierarchy for PRO data analysis can be found in this addendum and are repeated below.

Secondary efficacy endpoints related to the PRO, and their testing order, are as follows:

- Mean change from baseline at Cycle 10 in BPI-SF Average Pain Intensity (API) score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL)
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Physical Functioning
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Role Functioning

The PROMIS questionnaire will not be formally tested in the endpoint hiearchy.

4.3.3. Exploratory and Other Supportive Efficacy Analyses

4.3.3.1. Best Overall Response (BOR)

Confirmed BOR (as reported from Central Imaging review) is defined as the best response obtained across all time points during the DB phase of the study provided after application of the following confirmation rules:

Rule 1: PR or CR require confirmation by a subsequent scan. To be allowed to confirm a PR or a CR, a time point must be at least 4 weeks after the initial PR or CR is observed.

Rule 2: To be assigned SD as a BOR, a participant is required to have at least one non-PD/non-Evaluable (NE) time point response at least 8 weeks after baseline and not meet requirements for BOR of PR or CR.

Rule 3: When one or more NE time points are interleaved between CR or PR time points, these NE time points will not impact response confirmation. As an example, a participant with PR-NE-PR will be assigned a BOR=PR (provided the second PR meets rule 1).

Table 6. BOR Determination Table

First Time Point Response	Subsequent Time Point Response	BOR
CR	CR*	CR
CR	PD	SD provided rule 2, otherwise PD
CR	NE	SD provided rule 2, otherwise NE
PR	PR* or CR*	CR if CR is confirmed; PR otherwise
PR	SD	SD
PR	PD	SD provided rule 2, otherwise PD
PR	NE	SD provided rule 2, otherwise NE
SD	SD	SD
SD	NE	SD provided rule 2, otherwise NE
SD	PD	SD provided rule 2, otherwise PD
NE	CR, PR, SD (and no subsequent response)	SD provided rule 2, otherwise NE
NE	NE	NE

Source: MICL Imaging Review Charter
Note: CR* or PR* indicates that time interval for confirmation must apply, see rule 1.

Confirmed BOR (as reported by central imaging review) will be summarized with frequency and two-sided 95% CI by treatment arm. A comparison between the two treatment arms will be performed using Cochran-Mantel-Haenszel test stratified by randomization factor.

4.3.3.2. Disease Control Rate (DCR)

DCR (CR+PR+SD) will be calculated for each treatment arm and the proportions will be compared using the Cochran-Mantel-Haenszel test stratified by randomization factor. The 2-sided 95% exact CI will also be presented

4.3.3.3. Time to Tumor Progression (TTP)

TTP is defined as the time from randomization until objective tumor progression; TTP does not include deaths. TTP will be compared between the two arms. Number of participants with progression, Kaplan-Meier quartiles (i.e., the 25th, 50th (median), 75th percentile estimates), as well as descriptive statistics will be presented by treatment arm.

4.3.3.4. PFS at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period

Proportion of participants with progression free survival at month 6, month 12 and month 24 of the treatment period will be compared between the treatment arms. Survival function estimates will be presented.

4.3.3.5. DOR at Month 6 (PFS6), Month 12 (PFS12) and Month 24 (PFS24) of Treatment Period

Proportion of participants who have experienced response who are still responders at month 6, month 12 and month 24 following the start of response will be compared between the treatment arms. Survival function estimates will be presented.

4.3.3.6. Time to Response

Time to first response and BOR will be calculated as time in months from first dose until date of either the first documented response (CR or PR) or BOR. Summary statistics will be provided by treatment arms.

4.3.3.7. Change in Tumor Volume Assessed by MRI

Percent change in tumor volume assessed by MRI will be analyzed using a repeated measures model adjusting for baseline tumor volume and randomization strata. The analysis will use mixed model with repeated measures (MMRM) and the model will include treatment, baseline volume, visit, and randomization strata as covariates. Treatment by visit interaction will be included in the model and if significant, treatment differences will be assessed by timepoint. The covariance structure will be assumed to be unstructured, although if the matrix fails to converge, alternative structures will be used in the following order until convergence is reached: Toeplitz with heterogeneity (TOEPH), autoregressive with heterogeneity (ARH[1]), Toeplitz (TOEP), and autoregressive (AR[1]). The assessment timepoints will be analyzed as categorical. The model will use a Kenward-Rogers approximation for the degrees of freedom. Adjusted mean estimates per treatment arm and 95% CIs along with an estimate of treatment difference, 95% CI, and p-value will be presented. In addition, unadjusted summary statistics for tumor volume will be presented by visit and treatment arm. The main analysis of change in tumor volume will focus solely on the largest target lesions per subject while an additional analysis will focus on lesions that have clinically progressed.

The same analysis will be repeated on the subset of participants who discontinued the study due to PI-determined clinical progression and adjudicated as qualified event for the primary analysis by the independent EAC. A listing of tumor volume for all PI-determined clinical progressions will also be provided.

Waterfall plots of the percent change from baseline in target tumor size by tumor volume as assessed by MRI will be presented by subject with each subject color-coded based on their best overall disease response.

4.3.3.8. Change in Sum of Largest Diameter of Tumor Assessed by RECIST

Observed value, change from baseline and percent change in sum of largest diameter of tumor accessed by RECIST will be summarized over scheduled visits by treatment arm and overall.

Sum of largest diameter is called as follows:

- The diameter of each lesion is assessed by two readers.
- The sum of the lesions is calculated from the tumors identified at baseline for each visit. New tumors will not be included in the sum.
- The average sum of lesions for the two readers is calculated unless the assessments were adjudicated. In cases where the assessments are adjudicated, the adjudicated (sum) record will be used.

The readings of tumor diameters accessed by RECIST will be listed in participant data listings.

Waterfall plots of the percent change from baseline in target tumor size by RECIST v1.1 will be presented by subject with each subject color-coded based on their best overall disease response. For the RECIST tumor size plot, the percent change from baseline will be computed on the averages of sum of target lesion diameters from the two readers for each subject.

4.3.3.9. Tumor Response by Exposure

The relationship between active treatment exposure (nirogacestat) and disease response (as measured by RECIST response categories) will be explored among the actively treated participants in the following manner (through modeling when appropriate):

1. Total exposure by response status will be compared. Total exposure is defined as the total number of equivalent cycles treated at per protocol dose during the treatment period. It is defined as

   Number of equivalent cycle = total dose administered / (28 * 300mg)

2. Actual and relative dose intensities (as defined in Sec 4.4.1 below) will be compared by response status
3. Correlation between exposure, as measured by total exposure and exposure intensity, and time to first response will be investigated through Cox modeling. HRs will be compared between participants with high (> median) or low (<= median) exposure.

4. Correlation between change in tumor size/volume and exposure (total and intensity) will be explored through linear regression modeling, adjusted for baseline tumor size/volume.
5. Comparison of time to response between patients who had dose reductions vs those who had not using Cox model.

4.3.3.10. Change in Tumor Volume by Tumor Response

Actual value and change from baseline in tumor volume will be summarized over scheduled visits by treatment arm and RECIST tumor response (PD, SD, and CR/PR).

4.3.3.11. Change in Symptoms by Exposure and Change in Tumor Size/Volume

Analysis has shown that the recently created GODDESS instruments for DT patients, Desmoid Tumor Symptom Scale (DTSS) and Desmoid Tumor Impact Scale (DTIS), having good psychometric properties. Therefore, the investigation of change in DT symptoms and impact as a function of active treatment exposure and change in tumor size/volume will focus on the scores of GODDESS and its subdomains, supplemented with scores from BPI and EORTC when appropriate. Descriptions of the instruments, item definitions and domain scale construction are provided in the PRO Addendum attached to this document.

a. Change in Symptoms by Change in Tumor Size/Volume

Correlation between symptom scores of GODDESS, BPI and EORTC and percent change in tumor size (per RECIST) / tumor volume (per MRI) will be calculated.

GODDESS subscales to consider:

DTSS Weekly Avg Mean Score	DTIS Physical Functioning Domain Score
DTSS Pain Domain Score	DTIS Sleep Domain Score
DTSS Extra-abdominal Domain Score (among participants with extra-abdominal tumor)	DTIS Emotional Domain Score
DTSS Intra-abdominal Domain Score (among participants with intra-abdominal tumor)	

BPI Subscales to consider:

BPI #3 (worst pain last 24 hrs)	BPI Pain Severity Subscale Score
BPI #5 (avg pain last 24 hrs)	BPI Pain Interference Subscale Score

EORTC Subscales to consider:

QLQ-C30 Physical Functioning	QLQ-C30 Cognitive Functioning
QLQ-C30 Role Functioning	QLQ-C30 Social Functioning
QLQ-C30 Emotional Functioning	QLQ-C30 Insomnia

b. DT Symptoms and Impact by Exposure

Difference in exposure levels (total and intensity) between responders and non-responders, as defined by clinical meaningful change in GODDESS scores and subscores, will be investigated for the overall (exposure during full double-blind period versus responder at any point in double-blind period) and within the first six cycles of the study treatment period (exposure through six cycles versus early responders through 6 cycles).

Similar comparisons will be carried out between participants who do or do not experience a clinically significant change in pain, as measured by a 2-point or more reduction in BPI #3 (worst pain in past 24 hrs).

4.3.3.12. PFS by Mutation Status in APC and CTNNB1 Genes

Besides descriptive statistics (frequency and distribution) and data listings, the relationship between germline and somatic mutation status of APC and CTNNB1 and PFS will be explored through Cox modeling.

4.3.3.13. Other Prognostic Factors

Besides genetic mutations in Section 4.3.3.12, stratified Cox proportional hazards model will be used to estimate HRs according to stratification factor and additional factors described in Section 3.6 and listed under Section 3.7 using a stepwise procedure. Possible interactions among those factors will also be explored.

4.3.3.14. Change in Expression of Notch Genes

Change between pre- and post-dose gene expression values of Notch pathway will be analyzed using mixed model. Data listing by participant will be provided. If data is not available by time of the primary analysis, this analysis will be carried out as a part of analysis at the end of OLE.

4.3.3.15. Change in MRI T2 intensity

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and overall. All MRI T2 hyperintensity results will be listed in participant data listings.

4.3.3.16. Change in MRI T2 intensity by Tumor Response

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and RECIST tumor response (PD, SD, and CR/PR). Change in MRI T2 intensity by Baseline T2 Intensity Category (90%+ vs <90%)

Actual value and change from baseline in MRI T2 hyperintensity will be summarized over scheduled visits by treatment arm and baseline T2 hyperintensity (<90% and ≥ 90%).

4.3.3.17. DT Specific Comorbidity

Comparison will be made between the treatment and placebo arms on the incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity which may include hospitalization as a result of small bowel obstruction, hospitalization due to desmoid

tumor-related pain, or surgery for desmoid tumor. The list of terms included in this analysis will be identified prior to unblinding for the primary analysis.

4.3.3.18. Local vs Central RECIST v1.1 Readings

A concordance analysis of RECIST v1.1 results by the local site investigators vs blinded central reviewers will be attempted. Cohen's kappa test will be conducted, whenever data available. If sufficient data is not available by time of the primary analysis data cut, this analysis will be carried out after last patient, last visit for the double-blind phase of the study.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population. All data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed and reported separately.

4.4.1. Study Drug Exposure and Compliance

Extent of exposure will be summarized for each treatment arm based on the Safety population.

Exposure will be summarized by treatment arm and overall, as follows:

- Duration of exposure in months (last dose date – first dose date + 1 / 30.4375) summarized as a continuous variable

  If a data cut-off date is used at the time of analysis and participants are receiving treatment, the last dose date will be the data cut-off date
- Number and percentage of participants who received treatment with a duration of at least 1 cycle, 2 cycles, 3 cycles, 6 to < 13 cycles, 13 cycles to <25 cycles and 25 cycles or longer
- Actual dose intensity (mg/day) – calculated as the cumulative dose received / duration of exposure based on dose modification data
- Relative dose intensity (%) defined as 100 x (total cumulative dose received)/ (planned cumulative dose, where planned cumulative dose is 300 mg/day multiplied by duration of exposure) and summarized as a continuous variable
- Number and percentage of participants per relative dose intensity group (< 80% vs ≥ 80%)
- Number and percentage of participants with a dose modification (dose reduction and/or dose interruption as reported on the dose modification eCRF) as well as reasons for dose modification
- Number and percentage of participants with a dose reduction (as reported on the dose modification eCRF)
- Time (in completed cycles) to the first dose reduction and first dose interruption will be summarized as continuous variables
- Number and percentage of participants with a dose interruption including the number of days interrupted (cumulative and per interruption)
- Number and percentage of participants with study drug discontinued

A by-participant listing will be presented for exposure to study drug and dosing modifications.

4.4.2. Adverse Events

All AEs will be coded using the MedDRA coding system version 24.0 or later and displayed in tables and data listings using system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent adverse events (TEAEs), where treatment-emergent is defined per protocol as any AE with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. The imputation of partial/missing dates is described in Section 7.1.

Treatment-related TEAEs are defined as a TEAE that was considered by the Investigator to be at least possibly related to the study drugs. If the 'Relationship to study drug' is missing, then it will be imputed as 'Related to study drug' in summary tables. AE severity will be classified according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

A summary of AEs by treatment arm and overall will include the number and percentage of participants who experience at least one of the following. The total number of events will also be reported.

- TEAEs
- TEAEs related to study treatment
- Serious TEAEs
- Serious TEAEs by Relatedness
- TEAEs with CTCAE grade ≥ 3
- TEAEs with CTCAE grade ≥ 3 related to study treatment
- TEAEs by maximum severity (Grade)
- TEAEs leading to early discontinuation from study
- TEAEs leading to death
- TEAEs by Cycle of Onset *
- Rash or Alopecia TEAEs+
- Ovarian Dysfunction Events (as defined by a narrow list of terms per Section 7.5.1) by resolution status (WOCBP only)+
- Diarrhea within the first 3 cycles+

***A Cycle of Onset is assigned to each TEAE based on 28-day windows starting from treatment start. TEAEs in first five cycles are displayed separately while all TEAEs occurring from Cycle 6 to Cycle 12, and Cycle 12 onward are presented together.**

+indicates these summaries will only be included in the overall summary of AEs and will not be summarized by SOC and PT

In each tabulation of TEAEs, each participant will contribute only once (i.e., the most related occurrence, or the most intense occurrence, or the first cycle of onset) to each of the subject incidence rates in the descriptive analysis, regardless of the number of episodes.

The above categories will also be presented in tables summarizing SOC and PT by treatment arm and overall. If a participant experiences multiple AEs under the same PT (or SOC), then the participant will be counted only once for that PT (or SOC). The number of events of each type will be displayed alongside associated subject incidence percentages.

A TEAE summary by PT only and sorted by descending frequency of the active treatment arm will also be produced.

All AEs will be listed in participant data listings.

By-participant listings will also be provided for the following: AEs leading to death, serious adverse events, and AEs leading to withdrawal or discontinuation from study.

4.4.2.1. Selected Treatment Emergent Adverse Events

Additional summary tables are planned for selected adverse events.

- Ovarian dysfunction (OD) [separately for Narrow terms and both Broad and Narrow identified per Section 7.5. –WOCBP only]:
    - Summary of participants and number of events of ovarian dysfunction overall, by treatment, and by age category (<35, 35-<40, 40+)
    - Summary statistics for time to onset of first OD event (days), duration of each event (days), and time from start of first OD to resolution of all OD (days) overall, by treatment and age category (<35, 35-<40, 40+)
    - Summary of OD event outcomes overall, by treatment, and by age category (<35, 35-<40, 40+). Percentages for this summary will be out of the total number of OD events
    - Summary of prior therapy including any prior therapy (systemic/radiation/surgical, yes/no), prior radiation therapy (yes/no), prior therapeutic surgery (yes/no), or prior systemic therapy (yes/no) in WOCBP with and without ovarian dysfunction. Additionally, type of prior systemic therapies, number of lines of prior systemic therapies will be summarized.
    - Relative Intensity during Double-Blind Phase in WOCBP with and without ovarian dysfunction
    - Summary of dose modifications (reduction, interruptions, withdrawal) in participants reporting events of OD overall and by treatment
    - Summary of concomitant medications initiated for the treatment of events of OD by ATC classification and PT, grade (Grade 1-2 vs 3+) overall and by treatment
    - Summary of duration of concomitant medication use for treatment of events of OD by grade (Grade 1-2 vs 3+) overall and by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.

- Diarrhea
    - Summary statistics for time to onset of first Diarrhea event (days), duration of each event (days), and time from start of first diarrhea to resolution of all diarrhea events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of diarrhea by ATC classification and PT by treatment, grade (Grade 1-2 vs 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs of diarrhea by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.
- Hypophosphatemia
    - Summary statistics for time to onset of first hypophosphatemia event (days), duration of each event (days), and time from start of first hypophosphatemia to resolution of all Hypophosphatemia events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of hypophosphatemia by ATC classification and PT, grade (Grade 1, 2, 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs of hypophosphatemia by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.
- Rash, Hidradenitis, and Hair Follicle AEs (separately for Narrow and both Broad and Narrow Terms identified in Section 7.5.2)
    - Summary statistics for time to onset, duration of event, and time to resolution by event grade (Grade 1, 2, 3+) and overall
    - Summary statistics for time to onset of first event (days), duration of each event (days), and time from start of first event to resolution of all events (days) overall and by treatment
    - Number and percentage of participants with each event outcome, and number and percentage of participants with each grade (Grade 1-2 vs 3+) overall by treatment
    - Summarize concomitant medications initiated for treatment of events by ATC classification and PT, grade (Grade 1, 2, 3+) overall and by treatment
    - Summarize duration of concomitant medication use for AEs by grade (Grade 1-2 vs 3+) overall by treatment. If multiple medications are received durations will be combined and days in which both medications are taken will be counted once.

4.4.2.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for this study are defined in Protocol Section 8.3.6 and include the following groups and descriptions:

- Skin Rash (clinically significant Grade 2 and Grade ≥ 3, per CTCAE v.5)
    1. Maculopapular rash
    2. Pruritic rash
    3. Erythematous rash
    4. Folliculitis
    5. Hidradenitis suppurativa
- Elevated Liver Enzymes (reported as AESI if Grade ≥ 2, per CTCAE v.5)
    1. Aspartate Aminotransferase
    2. Alanine Aminotransferase
    3. Alkaline Phosphatase
- Electrolyte Insufficiency (Grade ≥ 3, per CTCAE v.5)
    1. Hypophosphatemia
    2. Hypokalemia
    3. Hypomagnesemia
- Drug Reactions (All grades)
    1. Allergic reaction
    2. Anaphylaxis
- Reproductive System Disorders (Grade ≥ 2, per CTCAE v.5)
    1. Amenorrhea
    2. Premature menopause / Primary ovarian insufficiency

Determination of whether an event is an AESI is based on investigator reported data. The incidence of AESI's will be summarized by AESI group and PT in tables and listed separately in participant data listings.

4.4.2.3. DT Specific Comorbidity

The incidence and frequency of clinical events related to disease specific desmoid tumor comorbidity will be summarized by treatment arm. More details are provided in Section 4.3.3.14.

4.4.3. Clinical Safety Laboratory Assessments

Central results will be the primary results to be analyzed. However, if a subject has local lab results collected during a scheduled visit and does not have central laboratory results collected for a parameter, the local results will be included for analyses. If a subject has both central and local laboratory results collected for a lab parameter during a scheduled visit, only the central results will be included for analyses. Central laboratory results from unscheduled visits will be used in the baseline and worst post-baseline derivations only. Local unscheduled visits are excluded from derivations and summarized results.

The actual value and change from baseline will be summarized for each visit for clinical laboratory parameters (hematology, chemistry, coagulation, and hormones) by treatment arm and overall.

Laboratory results will also be summarized by maximum CTCAE grade as available. For lab tests with NCI – CTCAE classification, the shift from baseline to maximum (worst) post baseline grade will be tabulated. Shift tables will summarize the count and frequency of each CTC grade to the highest CTC grade on study and where appropriate for the lab test, will include shifts to abnormal high values or abnormal low values. Laboratory tests with bi-directional grades will be presented separately for each direction (e.g., hyperglycemia and hypoglycemia). For lab tests without NCI – CTCAE classifications, the shift from baseline to each post baseline visit as well as the shift to the worst value will be summarized using the lab range indicators (normal, high, or low).

Additional shift tables will be produced for ALT, AST, alkaline phosphatase, bilirubin, phosphorus, and creatine showing shifts from below normal range, within normal range, >1 to 2 × upper limit of normal range, >2 to 3 × upper limit of normal range, >3 to 5 × upper limit of normal range and > 5 × upper limit of normal range to the worst (highest) post baseline value. Analysis related to hormone levels will be presented according to sex and by childbearing potential for female participants.

Box and whiskers plots displaying the values over time by nominal visit will be produced for each lab test. Hormone parameters will be displayed separately by sex. Additionally, WOCBP and Women who are not of childbearing potentially will be displayed separately. WOCBP will also be displayed by OD status and treatment.

All laboratory results will be listed and laboratory tests with an abnormal result will be listed separately. A subset listing will be presented for all grade 3 or higher laboratory values. A listing of participants with AST or ALT > 3X ULN that occurred within 2 days of a bilirubin value >2 ULN will be presented.

Serum pregnancy testing data will be presented for each participant in a data listing.

4.4.4. Physical Examinations and Eastern Cooperative Oncology Group Performance Status

Physical examination abnormalities reported as AEs will be summarized along with other TEAEs.

Shift tables by treatment arm and overall will summarize the count and frequency for each shift of baseline ECOG performance status grade to worst post-baseline ECOG grade. Similar tables will be provided for shifts to better grades. The ECOG performance status grades are outlined in Table 7.

All physical examination findings and ECOG performance status results will be presented in data listings.

Table 7. Eastern Cooperative Oncology Group Performance Status Grades

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

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

4.4.5. Electrocardiogram

The actual value and change from baseline at each time point will be summarized for 12-lead ECG parameters by treatment arm and overall. The triplicated 12-Lead ECG parameters include heart rate, PR, RR, QRS, QT and QTcF intervals. The data presented represents the average values from the triplicate ECGs.

Categorical groups of QTcF will be summarized as follows:

- Maximum post-baseline QTcF
  - ≤ 450 msec
  - > 450 and ≤ 480 msec
  - > 480 and ≤ 500 msec
  - > 500 msec
- Maximum change from baseline for QTcF
  - ≤ 30 msec
  - > 30 and ≤ 60 msec
  - > 60 msec

All ECG data will be included in a by-participant data listing. Listings will be provided for participants with abnormal or outlying values for QTcF and changes in QTcF.

4.4.6. Vital Signs

The actual value and change from baseline for all parameters (except height) will be summarized at each scheduled visit by treatment arm and overall.

Vital sign measurements will be presented for each participant in a data listing.

4.4.7. Concomitant Medications and Procedures

Concomitant medications and procedures will be coded using the WHO Drug Dictionary and are defined as any medication or procedure that did not end prior to first dose or start after the 30-day follow-up period. The handling of partial/missing start dates for concomitant therapies/medications are described in Appendix 7.2. PTs will be modified to be grouped as outlined in Appendix 7.4 to consolidate brand and generic medication names for the same active ingredient into a single line item to facilitate reporting of the same medication. Both the original and modified PTs will be included in the listings. Concomitant medications will be tabulated by anatomic therapeutic class (ATC) and modified PT by treatment arm and overall. In these tabulations, each participant will contribute only once to each ATC and modified PT regardless of number of uses.

Medications will be considered prior if they stopped before the first dose of study drug. Prior medications will be tabulated separately from concomitant medications.

All medications and procedures will be included in separate data listings; an identifier will be used to show whether a medication/procedure was prior or concomitant. Both original PT and modified PT will be presented on the listing.

4.5. Pharmacokinetic and Pharmacodynamic Analyses

A separate supplementary SAP will describe the PK parameters, PopPK/PD models, and analyses. Plasma pharmacokinetic collection dates, times, and concentration results will be displayed in a data listing.

5. CHANGES TO PLANNED ANALYSES

Notable changes from the protocol-defined statistical analyses compared to this statistical analysis plan are described below:

I. An interim analysis is no longer planned

II. "Change in tumor volume from baseline as assessed by MRI volumetric" has been moved from secondary to exploratory endpoint, per FDA comment

III. "Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks" has been moved from secondary to exploratory endpoint (as described in the PRO Addendum), due to duplications to other PROs.

IV. Duration of Response and Duration of Stable disease have been removed from the hierarchical testing of secondary endpoints as they are considered supportive of ORR.

V. Proportion of participants with improvement in BPI-SF API score at Cycle 10 has been removed from the hierarchical testing of secondary endpoints.

VI. Estimates of duration of response at Months 6, 12 and 24 have been added.

6. REFERENCES

Guo C, So Y, and Johnston G. Analyzing Interval-Censored Data with the ICLIFETEST Procedure. 2014. https://support.sas.com/resources/papers/proceedings14/SAS279-2014.pdf

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

European Medicines Agency. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. 2021 April 02 (Version 4.0).

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-556.

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

The ICLIFETEST Procedure:
https://documentation.sas.com/doc/en/statug/15.2/statug_iclifetest_toc.htm

US Food and Drug Administration. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020 (Updated Jan 2021).

7. APPENDICES

7.1. Handling of Missing/Partial Dates for AEs

Adverse events with incomplete onset dates will be handled as follows for the purpose of determining treatment emergence.

If the start date is partially missing, the date will be compared to the start of administration of study drug and the end date of administration+30 days.

1. If the month and day are missing:
   - If the year of the event is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
   - If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
   - If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.
2. If the day is missing:
   - If the month and year are the same as the month of treatment, the onset date will be assigned to the date of treatment.
   - If the month and year are not the same as the month/year of treatment, then the onset day will be set to the first day of the month.

If the start date is completely missing and end date is not before the first dose of study drug, then the adverse event will be considered treatment emergent.

If the participant has died and the imputed date is later than the date of death, the date of death will be used.

7.2. Handling of Missing/Partial Dates for Concomitant Therapies/Medications

Concomitant therapies/medications with start dates that are completely or partially missing will be handled as follows for the propose of determining concomitance.

1. If the start date has the month and year but the day is missing, the therapy will be considered concomitant if the month and year are:
   a. On or after the month and year of the date of the first dose of study drug
   b. On or before the month and year of the date of the last dose of study drug plus 30 days
2. If the start date has the year, but the day and month are missing, the therapy will be considered concomitant if the year is:
   a. On or after the year of the date of the first dose of study drug

b. On or before the year of the date of the last dose of study drug plus 30 days.

3. If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is prior to the date of the first dose of study drug, then this therapy will not be considered concomitant.
4. If the start date of concomitant therapies is completely or partially missing and the stop date of concomitant therapies is on or after the date of the first dose of study drug, then the therapy will be considered concomitant.
5. If the start date and stop date of concomitant therapies are completely missing, then the therapy will be considered concomitant.

7.3. Handling of Missing Dates for Disease History and Prior Therapies

For the purpose of calculating time from diagnosis or most recent prior therapy to randomization, partial/missing dates for diagnosis and last prior therapy completion will be imputed as follows:

- If both day and month are missing and the year is prior to the year of screening, the imputed day and month will be 01 July.
- If both day and month are missing and the year is the same as the year of screening, the imputed date will be the middle point between 01 Jan of the year and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- If day is missing and the month and year are prior to the month and year of screening, the imputed date will be 15th day of the month.
- If day is missing and the month and year are the same as the month and year of screening, the imputed date will be the middle point between the first date of the month and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- No imputation will be performed if the year is missing.

7.4. Consolidated Medication Coding

Consistent with standard conventions for coding concomitant medications using WHO Drug preferred terms, the coded term for certain medications varies based on whether the reported verbatim term was a brand name or generic name. To facilitate data reporting for the same medication, the coded terms for brand and generic named medications will be consolidated in summary tables. WHO Drug preferred terms will be combined as outlined below. For all terms not listed, the original coded term will be used. Both the original and consolidated terms can be found in the datasets.

Original Term(s)	**New Term**
Morphine sulfate MS Contin	morphine sulfate
Loperamide Hydrochloride	Loperamide
Ketorolac Tromethamine	Ketorolac
Cyclobenzaprine Hydrochloride	Cyclobenzaprine
Venlafaxine Hydrochloride	Venlafaxine
Ciprofloxacin Hydrochloride	Ciprofloxacin
Levothyroxine Sodium	Levothyroxine
Prochlorperazine Edisylate Maleate	Prochlorperazine
Cetirizine hydrochloride	Cetirizine
Diphenhydramine Hydrochloride	Diphenhydramine
Valaciclovir Hydrochloride	Valacyclovir
Oxycodone Hydrochloride	Oxycodone
Pantoprazole sodium sesquihydrate	Pantoprazole
Macrogol 3350	Macrogol
Tramadol HCL	Tramadol
Metamizole Sodium	Metamazole
Imatinib mesylate	Imatinib
Sorafenib Tosilate	Sorafenib
Tegavivint	Tegatrabetan
Vinblastine Sulfate	Vinblastine
Vinorelbine tartrate	Vinorelbine

7.5. Preferred Terms for Adverse Event Analyses

7.5.1. Ovarian Dysfunction (OD)

The following list of preferred terms will serve to identify which WOCBP who are participating in studies of nirogacestat are of interest for additional analyses of the potential for nirogacestat to disrupt ovarian follicular cycling. Narrow terms are considered the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad."

Table 8. Broad Summary of Preferred Terms to Describe Ovarian Dysfunction in WOCBP

MedDRA Code	PT	HLT	SOC
10085424	Abnormal uterine bleeding	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10001928	Amenorrhoea[1]	Menstruation with decreased bleeding	Reproductive system and breast disorders
10002659	Anovulatory cycle	Female gonadal function disorders	Endocrine disorders
10075158	Anti-Muellerian hormone level decreased	Reproductive hormone analyses	Investigations
10075597	Antral follicle count low	Fertility analyses	Investigations
10003439	Artificial menopause[1]	Menopausal effects NEC	Reproductive system and breast disorders
10003693	Atrophic vulvovaginitis	Menopausal effects on the genitourinary tract	Reproductive system and breast disorders
10005104	Bleeding anovulatory	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10063241	Blood gonadotrophin releasing hormone increased	Hypothalamic analyses	Investigations
10005687	Blood oestrogen decreased	Reproductive hormone analyses	Investigations
10014757	Endometrial hypoplasia[1]	Uterine disorders NEC	Reproductive system and breast disorders
10065596	Female sex hormone level abnormal	Reproductive hormone analyses	Investigations
10071084	Follicle stimulating hormone deficiency	Anterior pituitary hypofunction	Endocrine disorders
10074538	Genital atrophy[1]	Reproductive tract disorders NEC (excl neoplasms)	Reproductive system and breast disorders
10060800	Hot flush	Peripheral vascular disorders NEC	Vascular disorders
10021033	Hypomenorrhoea	Menstruation with decreased bleeding	Reproductive system and breast disorders
10021928	Infertility female	Sexual function and fertility disorders NEC	Reproductive system and breast disorders
10062020	Infertility tests abnormal	Fertility analyses	Investigations
10071083	Luteinising hormone deficiency	Anterior pituitary hypofunction	Endocrine disorders
10067371	Menopausal depression[1]	Depressive disorders	Psychiatric disorders
10058825	Menopausal disorder[1]	Menopausal effects NEC	Reproductive system and breast disorders

MedDRA Code	PT	HLT	SOC
10027304	Menopausal symptoms[1]	Menopausal effects NEC	Reproductive system and breast disorders
10027327	Menstrual disorder	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10027336	Menstruation delayed	Menstruation with decreased bleeding	Reproductive system and breast disorders
10027339	Menstruation irregular	Menstruation and uterine bleeding NEC	Reproductive system and breast disorders
10030229	Oestradiol decreased	Reproductive hormone analyses	Investigations
10030236	Oestriol decreased	Reproductive hormone analyses	Investigations
10030247	Oestrogen deficiency	Endocrine abnormalities of gonadal function NEC	Endocrine disorders
10030255	Oestrogens total urine decreased	Reproductive hormone analyses	Investigations
10063268	Oestrone decreased	Reproductive hormone analyses	Investigations
10030295	Oligomenorrhoea	Menstruation with decreased bleeding	Reproductive system and breast disorders
10033122	Ovarian atrophy[1]	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10033141	Ovarian disorder[1]	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10033165	Ovarian failure[1]	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10033310	Ovulation delayed	Female gonadal function disorders	Endocrine disorders
10067490	Ovulation disorder	Ovarian and fallopian tube disorders NEC	Reproductive system and breast disorders
10036601	Premature menopause[1]	Menopausal effects NEC	Reproductive system and breast disorders
10067168	Ultrasound ovary abnormal	Reproductive organ and breast imaging procedures	Investigations
10047791	Vulvovaginal dryness	Vulvovaginal signs and symptoms	Reproductive system and breast disorders
10027308	Menopause[1]	Age related factors	Social circumstances

1. Term is both a broad and narrow term

7.5.2. Rash, Hidradenitis, Hair Follicle AEs

7.5.2.1. Rash

The following list of preferred terms is intended to identify patients participating in studies of nirogacestat who experienced adverse generalized rash-like skin events but excluding events due to the possible effects of nirogacestat on hair follicles. Narrow terms are considered to be the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad."

Table 9. Broad Summary of Preferred Terms to Describe Rash

MedDRA Code	PT	HLT	SOC
10037898	Rash vesicular	Rash vesicular	Rashes, eruptions and exanthems NEC
10037890	Rash scarlatiniform	Rash scarlatiniform	Rashes, eruptions and exanthems NEC
10057984	Rash rubelliform	Rash rubelliform	Rashes, eruptions and exanthems NEC
10037087	Pruritus	Pruritus	Pruritus NEC
10037884	Rash pruritic[1]	Rash pruritic	Rashes, eruptions and exanthems NEC
10037876	Rash papular[1]	Rash papular	Rashes, eruptions and exanthems NEC
10037870	Rash morbilliform[1]	Rash morbilliform	Rashes, eruptions and exanthems NEC
10050004	Rash maculovesicular	Rash maculovesicular	Rashes, eruptions and exanthems NEC
10037868	Rash maculo-papular[1]	Rash maculo-papular	Rashes, eruptions and exanthems NEC
10037867	Rash macular[1]	Rash macular	Rashes, eruptions and exanthems NEC
10015150	Erythema[1]	Erythema	Erythemas
10037855	Rash erythematous[1]	Rash erythematous	Rashes, eruptions and exanthems NEC
10037844	Rash[1]	Rash	Rashes, eruptions and exanthems NEC
10075807	Nodular rash[1]	Nodular rash	Rashes, eruptions and exanthems NEC
10056671	Mucocutaneous rash	Mucocutaneous rash	Rashes, eruptions and exanthems NEC
10037879	Rash papulosquamous[1]	Rash papulosquamous	Papulosquamous conditions
10037888	Rash pustular	Rash pustular	Skin structures and soft tissue infections
10037578	Pustule	Pustule	Skin structures and soft tissue infections
10064579	Exfoliative rash	Exfoliative rash	Exfoliative conditions
10040844	Skin exfoliation	Skin exfoliation	Exfoliative conditions
10012456	Dermatitis exfoliative generalised	Dermatitis exfoliative generalised	Exfoliative conditions
10012455	Dermatitis exfoliative	Dermatitis exfoliative	Exfoliative conditions
10047111	Vasculitic rash	Vasculitic rash	Skin vasculitides
10037857	Rash follicular[1]	Rash follicular	Pustular conditions
10012431	Dermatitis[1]	Dermatitis	Dermatitis and eczema
10082985	Erythrodermic atopic dermatitis	Erythrodermic atopic dermatitis	Exfoliative conditions
10012432	Dermatitis acneiform	Dermatitis acneiform	Acnes
10000496	Acne	Acne	Acnes
10000501	Acne conglobata	Acne conglobata	Acnes
10000503	Acne cystic	Acne cystic	Acnes
10000513	Acne pustular	Acne pustular	Skin structures and soft tissue infections
10013786	Dry skin	Dry skin	Dermal and epidermal conditions NEC

1. Term is both a broad and narrow term

7.5.2.2. Hidradenitis

The following list of preferred terms is intended to identify patients participating in studies of nirogacestat who experienced adverse events due to the possible effects of nirogacestat on hair follicles and sweat glands, e.g., hidradenitis. Narrow terms are considered to be the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad."

Table 10. Broad Summary of Preferred Terms to Describe Rash

MedDRA Code	PT	HLT	SOC
10020040	Hidradenitis[1]	Hidradenitis	Apocrine and eccrine gland disorders
10055027	Sweat gland infection	Sweat gland infection	Apocrine and eccrine gland disorders
10000318	Abscess sweat gland	Abscess sweat gland	Skin structures and soft tissue infections
10018736	Groin sinus excision	Groin sinus excision	Abdominal therapeutic procedures NEC
10050269	Groin abscess	Groin abscess	Infections NEC

1. Term is both a broad and narrow term

7.5.2.3. Hair Follicle AEs

The following list of preferred terms is intended to identify patients participating in studies of nirogacestat who experienced adverse skin events due to the possible effects of nirogacestat on hair follicles. Narrow terms are considered to be the most specific or "narrow." The remaining terms can contribute to a sensitivity analysis and are considered to be "broad".

Table 11. Broad Summary of Preferred Terms to Hair Follicle Adverse Events

MedDRA Code	PT	HLT	SOC
10066409	Staphylococcal skin infection	Staphylococcal skin infection	Staphylococcal infections
10052891	Skin bacterial infection	Skin bacterial infection	Bacterial infections NEC
10037637	Pyoderma streptococcal	Pyoderma streptococcal	Streptococcal infections
10037632	Pyoderma	Pyoderma	Skin structures and soft tissue infections
10017553	Furuncle[1]	Furuncle	Staphylococcal infections
10007247	Carbuncle	Carbuncle	Skin structures and soft tissue infections
10042343	Subcutaneous abscess	Subcutaneous abscess	Skin structures and soft tissue infections
10016936	Folliculitis[1]	Folliculitis	Bacterial infections NEC
10015988	Eyelid infection	Eyelid infection	Eye and eyelid infections
10057211	Eyelid folliculitis	Eyelid folliculitis	Skin structures and soft tissue infections
10015980	Eyelid boil	Eyelid boil	Eye and eyelid infections
10000297	Abscess of eyelid	Abscess of eyelid	Eye and eyelid infections
10030261	Oil acne	Oil acne	Acnes
10012432	Dermatitis acneiform	Dermatitis acneiform	Acnes
10000518	Acne varioliformis	Acne varioliformis	Acnes
10000511	Acne occupational	Acne occupational	Acnes
10000507	Acne infantile	Acne infantile	Acnes
10049141	Acne fulminans	Acne fulminans	Acnes
10000503	Acne cystic	Acne cystic	Acnes
10000502	Acne cosmetica	Acne cosmetica	Acnes
10000501	Acne conglobata	Acne conglobata	Acnes
10000496	Acne	Acne	Acnes
10037888	Rash pustular[1]	Rash pustular	Skin structures and soft tissue infections
10037578	Pustule[1]	Pustule	Skin structures and soft tissue infections
10020377	Hordeolum	Hordeolum	Eye and eyelid infections
10001760	Alopecia[1]	Alopecia	Alopecias
10073736	Diffuse alopecia[1]	Diffuse alopecia	Alopecias
10001767	Alopecia universalis[1]	Alopecia universalis	Alopecias
10001766	Alopecia totalis[1]	Alopecia totalis	Alopecias
10001761	Alopecia areata[1]	Alopecia areata	Alopecias

1. Term is both a broad and narrow term

8. CLINICAL STUDY REPORT APPENDICES

8.1. Statistical Tables, Figures and Listings to be Generated

The Table of Contents for full list of tables, figures and listings can be found in a separate document (NIR-DT-301 TFL Table of Contents.pdf).