TITLE PAGE

A PHASE 2 TRIAL OF NIROGACESTAT IN PATIENTS WITH RECURRENT OVARIAN GRANULOSA CELL TUMORS

Protocol Number:	NIR-OGT-201
Amendment Number:	5
Compound Number:	PF-03084014 (nirogacestat)
Study Phase:	Phase 2
Short Title:	Nirogacestat in Ovarian Granulosa Cell Tumors
Sponsor Name:	SpringWorks Therapeutics, Inc.
Legal Registered Address:	100 Washington Blvd, Stamford, CT 06902, United States

Regulatory Agency Identifying Number(s):	Registry	ID
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	EU CT number	2023-510239-12-00

Approval Date	19Mar2024

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INVESTIGATOR'S AGREEMENT

I have read the protocol entitled, "A Phase 2 Trial of Nirogacestat in Patients With Recurrent Ovarian Granulosa Cell Tumors" dated 19Mar2024 and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation Guidelines for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines and any local regulations per country.

I agree to ensure that the confidential information contained in the protocol will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of SpringWorks Therapeutics.

This protocol has been received for information only and must be implemented before all necessary regulatory agency and Ethics Committee / Institutional Review Board approval documents have been obtained.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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SPONSOR'S SIGNATORY

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21-Mar-2024 | 11:17:45 EDT

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PPD

21-Mar-2024 | 13:14:33 EDT

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1: Document History

Document	Date
Amendment 5	19 March 2024
Amendment 4	07 June 2023
Amendment 3	31 January 2023
Amendment 2	18 July 2022
Amendment 1	13 December 2021
Original Protocol	09 November 2021

Amendment 5 (19Mar2024)

Full description of all changes to the protocol can be found in the Summary of Rationale and Changes document.

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Protocol title: A Phase 2 trial of Nirogacestat in Patients with Recurrent Ovarian Granulosa Cell Tumors

Short title: Nirogacestat in Ovarian Granulosa Cell Tumors

Rationale:

Epidemiology

Ovarian granulosa cell tumors (OvGCTs) represent 5-7% of all ovarian cancers (~1.5 to 2k newly diagnosed patients/year in the United States (US)) and are the most common subtype of ovarian sex cord tumors (70%). The average age at diagnosis for OvGCT is 50 years: 12% of OvGCT patients are younger than 30 years and 57% are between the ages of 30 and 59 years (Torre et al. 2018). OvGCTs are usually slow growing and often do not lead to mortality, so prevalence is high relative to incidence. In a 2018 case series (Dridi et al. 2018), mean overall survival (OS) was 13 years (11–15 years) from time at diagnosis with a 10-year OS of 90%. OvGCTs tend to recur late after primary surgery and primary platinum-based therapy. The recurrence rate in case series was 32% to 44% (longest reported time to recurrence was 40 years). Median recurrence free survival was 8.4 years (6.8–9.9 years) (Dridi et al. 2018).

Clinical Description and Presentation

OvGCTs originate from early ovarian mesenchyma and are composed of granulosa cells, theca cells, and fibroblasts.

Hyperestrogenism is reported in patients with OvGCT and is related to tumor production of estrogens, anti-Müllerian hormone (AMH), and inhibin A and B. This hormone production differentiates OvGCT from serous ovarian cancer and could serve as a tumor-specific pharmacodynamic marker.

A 2018 case series (Dridi et al. 2018), detailing 31 patients describes that sixty-one percent of cases presented with abdominal mass and/or abdominal pain, while postmenopausal bleeding was reported in 32% of cases. All cases underwent ultrasound imaging which showed mainly cystic unilateral masses in 80% of patients with a mean tumor size of 20cm (4-33cm). Significantly elevated levels of CA-125 were reported in 42% of OvGCT patients. Histologically, these tumors consisted of micro/macrofollicles with cores “coffee bean” (74%), Call-Exner bodies (55%), and necrosis (22%) – mitotic index measured in only 22 patients was mainly low (64%). Local pelvic recurrence was seen in 70% of cases – only 9% of recurrences were abdominopelvic, 6% were retroperitoneal, 6% were pelvic and retroperitoneal, and 3% were abdominopelvic and retroperitoneal. Metastatic locations were mainly liver (67%) and pleura (33%).

Standard of Care and Unmet Need

There are currently no Food and Drug Administration (FDA) approved therapies for OvGCT. Surgery, possibly with adjuvant chemotherapy, is the mainstay of initial treatment. Adjuvant

chemotherapy is typically with a platinum-based regimen: paclitaxel-carboplatin, cyclophosphamide-cisplatin, or bleomycin-etoposide-cisplatin. In the relapsed setting, which is the subject of this protocol, multiple chemotherapy regimens are used. These chemotherapy regimens are predominantly platinum based. After platinum, options are limited. One such example is bevacizumab. Bevacizumab used as single agent or in combination with chemotherapy (taxane or doxorubicin) in post-platinum recurrence has only modest activity (Gershenson, Okamoto, and Ray-Coquard 2019). A randomized trial in recurrent OvGCT evaluating paclitaxel (N=32) vs. paclitaxel + bevacizumab (N=28) showed only modestly improved activity with the combination of paclitaxel +bevacizumab. Paclitaxel monotherapy had an Objective Response Rate (ORR) of 25% (95% CI: 12-43%). Although the addition of bevacizumab increased the ORR to 44% (95% CI: 26-65%) no improvement in Progression Free Survival at 6 months (PFS-6) was seen. PFS-6 of paclitaxel + bevacizumab was 72% (95% CI: 57-89%) vs. PFS-6 of paclitaxel monotherapy of 71% (95% CI: 53-84%) in the trial (Ray-Coquard et al. 2020). Hormonal therapy (HT) has also been used in recurrent OvGCT and has shown some activity albeit inferior to that of paclitaxel. A retrospective analysis of HT (Meurs et al. 2015) showed an ORR of 18% with PFS and disease specific survival of 10 and 36 months respectively.

ORR from any monotherapy in the relapse setting is low. Furthermore, combination therapy in the relapse setting has failed to show an improvement in PFS rates. Therefore, there is an unmet need in this patient population for an agent with a higher response rate and the potential to improve PFS.

Scientific Rationale

NOTCH, particularly NOTCH-2 and 3, is an essential pathway for embryonic development of the ovary and function of the ovarian follicle (essential for development of mature oocytes and production of steroid hormones). Notch expression and function is important throughout follicle development and is an integral component of granulosa cell development, proliferation and function (Vanorny and Mayo 2017). Knockout or inhibition of Notch or Notch-related signaling genes in mice leads to poorly developed ovaries and/or development of primary ovarian failure (POF). Mutations in the Notch pathway (NOTCH-2, NOBOX, FOXO1, FOXO3, PTEN, WNT4 and FOXL2) have been associated with primary ovarian insufficiency (POI) and POF in humans. (Qin et al. 2007; Fortuño and Labarta 2014; Grzechocińska et al. 2019) Notch activation induces granulosa cell tumor proliferation while decreasing apoptotic cell death (Irusta et al. 2013). Inhibition of Notch by DAPT (r N-[N-(3,5- difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester), a γ-secretase inhibitor, in KGN cells (steroidogenic human granulosa-like tumor cell line harboring the FOXL2 C134W mutation) led to a decrease in proliferation and activation of apoptosis pathways via inhibition of PI3K/AKT signaling.

FOXL2 is the most important gene implicated in the development of OvGCT with more than 97% of OvGCT having a mutation in FOXL2 [C402G; C134W] (Li et al. 2018). An autosomal gene, FOXL2 is a transcription factor and member of the forkhead-winged helix family and, is one of the earliest known markers of ovarian differentiation. FOXL2 is required for normal development and function of granulosa cells (mainly expressed in undifferentiated granulosa cells) and is involved in ovarian granulosa cell proliferation, follicle development and ovarian hormones synthesis. The wild-type FOXL2 protein may also act as a tumor suppressor under certain circumstances by inducing apoptosis in damaged granulosa cells,

increasing DNA repair, slowing the cell cycle and suppressing growth factor signaling (Caburet et al. 2012; Benayoun et al. 2010). Li et al. (2018) has shown that overexpression of FOXL2 induces apoptosis in ovarian cells (including granulosa cells). STAT3, a likely transcription factor for FOXL2 (Han et al., 2017), is activated in the presence of active Notch and the Notch effector proteins hairy and enhancer of split (Hes) which facilitate complex formation between JAK2 and STAT3 (Kamakura et al, 2004). Therefore, activation of Notch signaling is directly involved in the expression of FOXL2 which may provide a check on notch-induced proliferation.

An in vitro study in granulosa and sertoli cell lines suggested that the ability of FOXL2 C134W to induce apoptosis in these cells is impaired (compared to WT) (Kim et al. 2011). Kim et al propose that the FOXL2 C134W transcription factor exhibits reduced expression of "death receptors" TNF-R1, Fas and TRAIL-R1. The reduced "death receptor" expression results in lower activation of the caspase apoptosis pathway. Granulosa cell proliferation and differentiation are governed, in part, by TGF-β receptor signaling through multiple SMAD proteins. Multiple receptor ligands, activins, inhibins, BMP, and AMH are involved. Both Notch Intracellular Domain (NICD) and FOXL2 interact with SMAD proteins to induce gene transcription.

An increase in growth factor (TGFβ) signaling in cells expressing the FOXL2 C134W mutant is believed to be due to a gain in SMAD function. In vitro studies indicate that FOXL2 C134W acquires the ability to bind to SMAD4, forming a complex with SMAD2/3 with a unique DNA binding motif leading to activation of TGFβ signaling and possibly driving proliferation of GCTs (Weis-Banke et al. 2020; Rosario et al. 2012).

Active Notch also Promotes Cell Proliferation through PI3K/AKT signaling

pAKT (via PI3K) is anti-apoptotic through inhibition of FOXO and Bcl-2 expression. Uncontrolled PI3K/AKT signaling in oocytes is oncogenic and has been shown to irreversibly develop granulosa cell tumors (GCTs). Negative regulation of PI3K occurs partly by the tumor suppressor PTEN (Li et al. 2018). PTEN mutation leads to over-phosphorylation and activation of AKT, thereby driving cell proliferation. HES1, a transcription product of activated Notch, is a repressor of PTEN. In the absence of HES1, PI3K is inactivated by PTEN (Li et al. 2018).

Therefore, treatment with of granulosa cell tumors with a gamma secretase (GS) inhibitor is expected to inhibit Notch-induced granulosa cell proliferation by (1) limiting activation of growth factor signaling by the FOXL2 mutant protein, (2) inhibiting proliferation signaling through NICD and (3) by inducing apoptosis through the pAKT activation.

Objectives and Endpoints	
Primary Objectives:	**Primary Endpoints:**
To determine the anti-tumor activity of nirogacestat in adult participants with relapsed/refractory OvGCT	Objective response rate, defined as the proportion of participants with Complete Response (CR) + Partial Response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary Objectives:	**Secondary Endpoints:**
To determine if nirogacestat delays progression or death in OvGCT	Estimate of proportion of participants who have not progressed or died at 6 months follow-up: PFS-6. Progression is defined by RECIST v1.1
To describe overall survival in participants treated with nirogacestat	Estimate of 2-year overall survival, defined as the proportion of participants who have not died after 2 years of follow-up after their first dose of nirogacestat
To determine the effect of nirogacestat on ovarian cancer symptoms measured by Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI)	Change from baseline in FOSI
To determine the duration of response	Duration of response (DoR), defined as the time from first assessment of response (CR + PR using RECIST v1.1) to first disease progression defined by RECIST v1.1 or death, whichever comes first
To determine the pharmacokinetics (PK) of nirogacestat	Serum concentrations of nirogacestat will be measured to evaluate system exposures (C_{max}, C_{trough} and other PK parameters as data allow)

Safety Objectives	Safety Endpoints
To characterize the safety and tolerability of nirogacestat at a dose of 150 mg BID in adult participants with relapsed/refractory OvGCT	Key safety endpoints will include incidence of treatment-emergent Adverse Events (TEAEs), changes in clinical laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs) Tolerability will be assessed according to toxicities graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Exploratory Objectives	**Exploratory Endpoints**
To detect FOXL2 C134W mutation as well as other genomic alterations and correlate these with response	Evaluate Next Generation Sequencing (NGS) status in baseline tumor tissue
To detect NICD and candidate biomarkers of response, and to correlate nirogacestat exposure with response	Evaluate change from Baseline: • Inhibin A&B, Follicle-stimulating hormone (FSH), estradiol, CA-125, and Müllerian Inhibiting Substance (MIS) / AMH • Circulating tumor DNA (ctDNA) Baseline NICD expression in tumor tissue
To describe progression free survival on continued nirogacestat treatment post first disease progression	Progression free survival on prolonged nirogacestat treatment, defined as time from first disease progression per RECIST v1.1 to second disease progression on continued nirogacestat treatment confirmed by investigator discretion or death, whichever comes first
To describe progression free survival on subsequent line of anticancer treatment	Progression free survival 2 (PFS2), defined as time from first dose of nirogacestat to second disease progression on subsequent line of anticancer treatment (after nirogacestat) confirmed by investigator discretion at long term safety follow-up visit or death, whichever comes first

Overall design: This is a multi-center, single-arm, Phase 2 open label treatment study to determine the efficacy, safety, tolerability, and pharmacokinetics of nirogacestat in adult participants with relapsed/refractory OvGCT. Participants must have received at least one prior course of systemic therapy for OvGCT and have measurable disease by RECIST v1.1 to meet the eligibility criteria.

Participants will be screened up to 28 days prior to the first dose of study treatment (nirogacestat) and full eligibility will be based on the inclusion and exclusion criteria (Sections 7.1 and 7.2).

Eligible participants will be enrolled in the study using the Interactive Response Technology (IRT) system following all pre-dose baseline assessments at Cycle 1 Day 1 (C1D1). Following C1D1, participants will return to the clinic for scheduled study visits monthly for the first year and then every 3 months thereafter until end of study participation.

Participants who discontinue study treatment early for any reason should return to the clinic for an End of Treatment (EOT) visit within 7 days after the Investigator determines study treatment will no longer be used and then again for a safety Follow-up (FUP) visit 30 days (+7 days) after the last dose of study treatment.

The estimated study duration is 3 years, and all participants will be followed for at least 2 years (unless the study is prematurely stopped due to futility).

A Bayesian strategy allowing continuous monitoring will be used to evaluate the posterior distribution of ORR (complete + partial) (J. Lee and Liu 2008; Chen et al. 2019) and the study may be stopped for futility if necessary. There will be no pause in accrual for interim assessments.

Disclosure Statement: Single-arm open label treatment study

Number of participants: Approximately 43 participants

Treatment groups and duration:

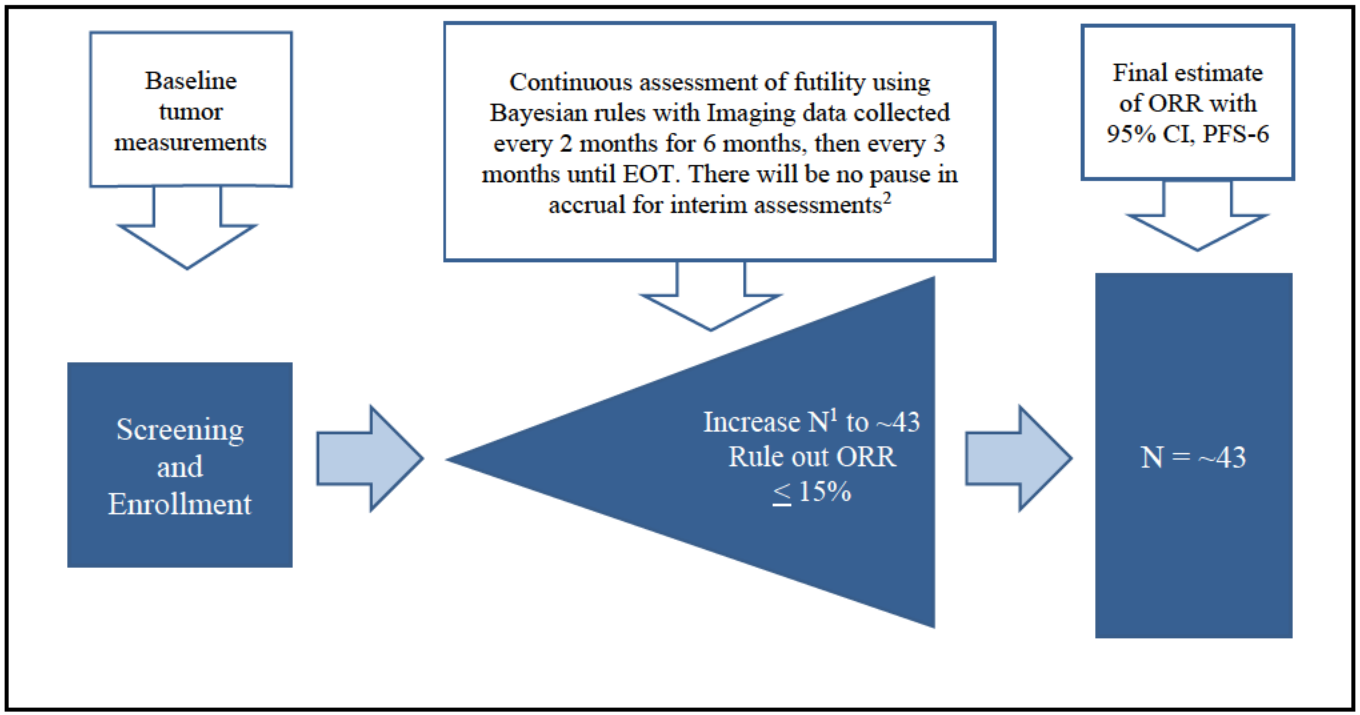
At C1D1 participants will be enrolled in the study using the IRT system and will receive 150 mg (orally) BID of study treatment (nirogacestat; 3 × 50 mg tablets), continuously in 28-day cycles.

Participants will remain on study treatment until death, disease progression (unless the participants meet criteria for continued treatment as defined in Section 9), discontinuation of study treatment for any reason, the study is stopped by the Sponsor for any reason, or participant qualifies for Sponsor's Compassionate Use Program.

Data Monitoring committee: No

1.2. SCHEMA

Figure 1: Schema



[1]Refer to Section 6.1 for more detail on accrual milestones.
[2]If the Response Rate falls below 15%, the study may be stopped for futility. See Table 11 for Probability of Early Stopping.

1.3. SCHEDULE OF ASSESSMENTS (SOA)

Table 2: Schedule of Assessments

Cycle Number/Day	**Screening**[1]	**C1D1 (Baseline)**[3]	**C2D1**	**C3D1, C4D1, C5D1, C6D1, C7D1**	**C8D1, C9D1, C10D1, C11D1, C12D1, C13D1**	**Cycle 16 & Every 3 Cycles (C16, C19, C22, etc.)**[23]	**EOT**[25]	**Safety FUP**[26]	**2-year Survival Check-In**[27]
Visit Week		**Week 1**	**Week 5**	**Weeks 9,13,17, 21,25**	**Weeks 29,33,37, 41,45,49**	**Weeks 61,73,85 & On**			**Week 104**
Calendar Day		*Day 1*	*Day 29*	*Days 57,85,113, 141,169*	*Days 197,225, 253,281,309, 337*	*Days 421,505,589 & On*			*Day 722*
(Visit Window)	*(Up to 28 days before Day 1)*	*(Up to 48 hours prior to 1st dose)*	*(±2 days)*	*(±2 days)*	*(±2 days)*	*(±7 days)*	*See footnote 25 for visit window*	*30 days after last dose (+7 days)*	*~2 years after first dose*
Informed consent[2]	X								
I/E criteria	X	X							
Demography	X								
Medical history including menstrual history	X								
ECOG performance status[4]	X	X	X	X	X	X	X	X	
Physical examination (including pelvic exam)[5]	X	X	X	X	X	X	X	X	
Vital signs[6]	X	X	X	X	X	X	X	X	
Weight/height[7]	X	X	X	X	X	X	X	X	
Single 12-lead ECG[8]	X	X[8a] *(post dose)*	X[8b] *(pre-& post dose)*				X	X	

Cycle Number/Day	**Screening**[1]	**C1D1 (Baseline)**[3]	**C2D1**	**C3D1, C4D1, C5D1, C6D1, C7D1**	**C8D1, C9D1, C10D1, C11D1, C12D1, C13D1**	**Cycle 16 & Every 3 Cycles (C16, C19, C22, etc.)**[23]	**EOT**[25]	**Safety FUP**[26]	**2-year Survival Check-In**[27]
Visit Week		**Week 1**	**Week 5**	**Weeks 9,13,17, 21,25**	**Weeks 29,33,37, 41,45,49**	**Weeks 61,73,85 & On**			**Week 104**
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(Visit Window)	*(Up to 28 days before Day 1)*	*(Up to 48 hours prior to 1st dose)*	*(±2 days)*	*(±2 days)*	*(±2 days)*	*(±7 days)*	*See footnote 25 for visit window*	*30 days after last dose (+7 days)*	*~2 years after first dose*
Laboratory									
Tumor biopsy[9] (archival or fresh)	X								
Blood for serology[10]	X								
Blood for PK sampling[11]			X[11a] *(pre - & post dose*	X[11b] *(pre-dose)*					
Blood for ctDNA biomarkers		X		X *(C3D1)*			X		
Blood for safety labs[12]	X	X	X	X	X	X	X	X	
Blood for hormone levels[13a]	X	X	X	X	X	X	X	X	
Blood for tumor markers[13b]		X	X	X	X	X	X	X	
Urinalysis[14]	X	X	X	X	X	X	X	X	
Blood/Urine for pregnancy test (WOCBP only)[15]	X *(serum)*[15a]	X *(urine)*[15b]	X *(urine)*[15c]	X *(urine)*[15c]	X ← *(monthly; urine)*[15.d] →		X *(urine)*[15c]	X *(urine)*[15c]	

Cycle Number/Day	**Screening**[1]	**C1D1 (Baseline)**[3]	**C2D1**	**C3D1, C4D1, C5D1, C6D1, C7D1**	**C8D1, C9D1, C10D1, C11D1, C12D1, C13D1**	**Cycle 16 & Every 3 Cycles (C16, C19, C22, etc.)**[23]	**EOT**[25]	**Safety FUP**[26]	**2-year Survival Check-In**[27]
Visit Week		**Week 1**	**Week 5**	**Weeks 9,13,17, 21,25**	**Weeks 29,33,37, 41,45,49**	**Weeks 61,73,85 & On**			**Week 104**
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Patient-Reported Outcomes (PROs)									
FOSI[16]	X	X	X	X	X	X	X	X	
Imaging									
CT or MRI scan for tumor measurement (using RECIST v1.1)[17a]	X			X *(C3D1, C5D1, C7D1)*	X *(C10D1, C13D1)*	X	X[17c]		
Chest imaging CXR/CT scan[17b]	X			X *(C3D1, C5D1, C7D1)*	X *(C10D1, C13D1)*	X	X[17c]		
Enrollment and Study Treatment									
Pre-Enrollment Review Form[18]	X								
Enrollment[19]		X							
Study treatment dispensing[20]		X	X	X	X	X			
Study treatment administration & Dosing Diary[21]		X ← →							

Cycle Number/Day	**Screening**[1]	**C1D1 (Baseline)**[3]	**C2D1**	**C3D1, C4D1, C5D1, C6D1, C7D1**	**C8D1, C9D1, C10D1, C11D1, C12D1, C13D1**	**Cycle 16 & Every 3 Cycles (C16, C19, C22, etc.)**[23]	**EOT**[25]	**Safety FUP**[26]	**2-year Survival Check-In**[27]
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Study treatment accountability			X	X	X	X	X		
Ongoing Monitoring									
ConMed review	X ← →								
AE/AESI/SAE review[22]	X ← →								
Remote monthly wellness checks[24]					X ← →				
Survival check-in[27]									← → X

AE = adverse event; AESI = adverse event of significant interest; BID = twice daily; ConMed = concomitant medication; ctDNA = circulating tumor DNA; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram;; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FOSI = Functional Assessment of Cancer Therapy – Ovarian Symptom Index; FUP = follow-up; ICF = informed consent form; I/E = inclusion/exclusion; MRI = magnetic resonance imaging; PK = pharmacokinetic; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SoA = schedule of assessments; v = version; WOCBP = women of child bearing potential.

Footnotes:

1. **Screening visit:** Assessments may occur up to 28 days prior to first dose of study treatment. An extension to the screening period may be permitted on a case-by-case basis following discussion between the Investigator and the Medical Monitor. The reason(s) for the extension must be clearly documented.

2. **Informed consent process:** Includes participant signing the Informed Consent Form (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 Appendix A1-3 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.
4. **ECOG performance status:** At Baseline, assessment must be done prior to first dose of study treatment. Refer to Appendix A4-2 for ECOG scale.
5. **Physical examination:** At Baseline, assessment must be done prior to first dose of study treatment. A pelvic exam is also required for participants whose disease can be evaluated by pelvic exam. Refer to Section 11.2.2 for detail regarding physical examination requirements.
6. **Vital signs:** Includes blood pressure, respiratory rate, heart rate, and body temperature (should follow at least 5 minutes of rest). At Baseline, assessment must be done prior to first dose of study treatment and should be done prior to blood draws when possible. Refer to Section 11.2.3 for more detail.
7. **Height/Weight:** Height is required at Screening only. A historical height measured within 1 year prior to signing informed consent may be used as the screening height. Weight to be collected at applicable study visits as described in the SoA.
8. **Single 12-lead ECGs:** ECGs will be collected as described in the SoA and read locally at the site. Participants should rest in a semi-recumbent supine position for at least 5 minutes prior to ECG collection and ECGs should be done after collection of vital signs when possible. Refer to Section 11.2.4 for more detail.
    a. C1D1: a single ECG is required 1-hour (±10 minutes) post-dose.
    b. C2D1: a single ECG is required pre-dose and 1-hour (±10 minutes) post-dose.
9. **Tumor biopsy:** At Screening, a core needle fresh biopsy is only required if archival tissue is not available for study procedures. If the archival tumor is used for the baseline sample, or if a fresh biopsy is collected, then sufficient tissue should be provided as a Formalin-Fixed Paraffin-Embedded (FFPE) block or FFPE unstained slides. If applicable, the fresh biopsy should be collected 7 or more days prior to first dose of study treatment. If tumor biopsy and imaging are performed on the same day, it is recommended that the biopsy is performed after imaging. Refer to the central laboratory manual for additional details.
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 Appendix A4-1 for details.
11. **PK sampling:** Refer to Section 11.5 and central laboratory manual for sample processing details. For all pre-dose PK samples, the evening before applicable study visits, participants will record the exact time study treatment was taken in the Dosing Diary. Participants will hold their planned morning dose of study treatment the day of the applicable pre-dose PK study visit and will take their dose after the pre-dose sample is collected.
    a. C2D1: a pre-dose PK sample is required prior to the morning dose of study treatment and a post-dose sample is required approximately 1-hour after the morning dose of study treatment.
    b. C3-C7: a pre-dose PK sample is required prior to the morning dose of study treatment.
12. **Safety Labs (hematology, serum chemistry):** At baseline, must be done prior to first dose of study treatment. Refer to Appendix A4-1 for a complete list of analytes.
13. **Hormone Levels and Tumor Markers**:
    a. Hormone Levels: Blood for FSH, LH, Estradiol and Progesterone will be obtained at specific times described in the SoA table. Baseline sample must be done prior to first dose of study treatment. Refer to the central laboratory manual for sample processing details.
    b. Tumor Markers: Blood for Inhibin A, Inhibin B, AMH/MIS and CA-125 will be obtained at specific times described in the SoA table. Baseline sample must be done prior to first dose of study treatment. Refer to the central laboratory manual for sample processing details.
14. **Urinalysis:** At Baseline, must be done prior to first dose of study treatment. Refer to Appendix A4-1 for a complete list of analytes. Microscopy is to be performed only as needed based on positive dipstick test results and only if blood or protein is abnormal.
15. **Serum / Urine pregnancy tests:** Only required for WOCBP participants. Throughout the study, serum pregnancy tests may be conducted in place of urine pregnancy tests if required by local regulations (sites should follow institutional standards). Refer to Section 11.2.6 for more detail.
    a. Screening: serum pregnancy test is required.
    b. Baseline (C1D1): urine pregnancy test is required prior to first dose of study treatment to reconfirm eligibility.
    c. C1-C13, EOT and FUP: urine pregnancy tests are required at each study visit.

d. Following C13: In between study visits, participants are required to return to the site for monthly (every 28 days [+/- 2 days]) urine pregnancy tests. 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.

16. **PROs:** Participants will complete the FOSI in the clinic at applicable study visits. When possible, the questionnaire should be given as the first assessment during the study visit to minimize participant bias. Refer to Section 11.1.2.1.
17. **Tumor imaging:** All scans will be performed and read locally. Same modality used at Screening must be used at each subsequent imaging visits. 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. On treatment scans may be performed (-) 7 days prior to the visit or within the study visit window as described in the SoA. Refer to Section 11.1.1 for more detail.
    a. Tumor imaging/measurement using RECIST v1.1: CT or MRI scans (contrast required unless contraindicated) will be acquired per the SoA to assess tumor changes. Tumor response and progression of cancer under study in real time will be evaluated locally at each study site according to RECIST v1.1. All RECIST measurements will be done by the site's local radiologist. Imaging must be done prior to tumor biopsy if assessments occur on the same day.
    b. Chest imaging: CXR or CT (contrast not required) required as described in the SoA and should be obtained per institutional standards.
    c. EOT Visit: Scans only required if not performed within the last 6 weeks.
18. **Pre-Enrollment Review Form:** This form should be submitted at least 2 days prior to C1D1 in order to allow the Medical Monitor to review and approve eligibility prior to the participant being enrolled in the Interactive Response Technology IRT system (refer to the study reference manual for additional details)
19. **Enrollment:** Participants will be enrolled during the C1D1 visit, using the IRT system, only after all baseline assessments have been completed and participant has been confirmed to meet all eligibility criteria.
20. **Study treatment dispensing**: Participants will be dispensed study treatment using the IRT every cycle for the first year (C1-C13) and then every 3 cycles thereafter.
21. **Study treatment administration/Dosing Diary**: The first dose of study treatment (3 × 50 mg tablets) will be administered orally at the site at C1D1 followed by a 1-hour observation period. Following the first dose, participants will self-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 Dosing Diary. Refer to Section 8 for more detail.
22. **AEs/AESIs/SAEs:** Will be monitored and documented from the time of informed consent up to 30 days after the last dose of study treatment. Participants reporting AEs/AESIs/SAEs of reproductive system disorders will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).
23. **Every 3 Cycles and On:** Following C13D1 participants will return every 3 cycles for study visits until end of study participation.
24. **Remote Monthly Wellness Checks:** Monthly (every 28 days [+/- 2 days]) telephone or email contact is required following C13D1 until EOT. The wellness checks may be replaced by a face-to-face interaction when study visits occur, provided the wellness information can be obtained during the visit. Refer to Section 11.2.7 for more detail.
25. **EOT visit:** The End of Treatment (EOT) visit should be conducted within 7 days after the Investigator determines that study treatment will no longer be used.
26. **Safety Follow-up (FUP):** The Safety FUP visit will be conducted 30 days (+ 7 days) after the last dose of study treatment.
27. **2-year Survival Check-In:** The final 2-year survival check-in will occur approximately 2 years after the first dose of study treatment. If participant discontinues from study treatment prior to the 2-year check-in, quarterly telephone or email contact following EOT is required until the 2-year survival data point has been collected. In addition, collection of subsequent anticancer therapy after nirogacestat and overall response to this therapy will be recorded. Only information about the subsequent therapy used directly after nirogacestat is required along with the final survival outcome at the 2-year check point. Refer to Section 11.2.8 for more detail.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 3: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AF	Aggressive Fibromatosis
AKT	Protein Kinase B
ALT	Alanine Aminotransferase
AMH	Anti-Müllerian Hormone
ANC	Absolute Neutrophil Count
ARAs	Acid Reducing Agents
AST	Aspartate Aminotransferase
BEP	bleomycin, etoposide, plus cisplatin
Bcl-2	B-cell lymphoma 2
BID	Twice daily
C	Cycle
CA 125	Cancer Antigen 125
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Creatinine Kinase Disease Epidemiology Collaboration
C_{max}	Maximum plasma concentration
C_{trough}	Plasma trough concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA

Abbreviation or specialist term	Explanation
CXR	Chest x-ray
CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytochrome P450 3A4
D	Day
DAPT	r N-[N-(3,5- difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DT	Desmoid tumor
DTP	Direct to Patient
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
Fas	Apoptosis antigen 1
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
FOXL2	Forkhead box protein L2
FOXO1	Forkhead box protein O1
FOXO3	Forkhead box protein O3
FSH	Follicle-stimulating hormone
FUP	Follow-up
GCP	Good Clinical Practice
GCT	Granulosa cell tumors
GOG	Gynecologic Oncology Group
GS	γ-secretase
H2	Histamine 2
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

Abbreviation or specialist term	Explanation
HCT	Hematocrit
HCV	Hepatitis C virus
Hes1	Hairy and Enhancer of Split 1
Hes4	Hairy and Enhancer of Split 4
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal Replacement Therapy
HT	Hormonal therapy
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HR	Heart rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
K-M	Kaplan-Meier
LD	Longest dimension
LDH	Lactate dehydrogenase
LH	Luteinizing Hormone
MIS	Müllerian Inhibiting Substance
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
N	Sample size
NE	Not evaluable
NGS	Next Generation Sequencing
NICD	Notch Intracellular Domain
No.	Number

Abbreviation or specialist term	Explanation
NOBOX	Newborn ovary homeobox protein
ORR	Objective Response Rate
OS	Overall survival
OvGCT	Ovarian granulosa cell tumors
PCR	Polymerase chain reaction
PD	Progressive Disease
PFS	Progression free survival
PFS2	Progression free survival 2
PFS-6	Progression free survival at 6 months
P-gp	P-glycoprotein
pH	potential Hydrogen
PI3K	Phosphoinositide 3-kinases
PK	Pharmacokinetics
PPI	Proton pump inhibitor
POF	Primary ovarian failure
POI	Primary ovarian insufficiency
PR	Partial Response
PRO	Patient-reported outcomes
PTEN	Phosphatase And Tensin Homolog
QD	Once daily
QRS	QRS complex
QT	Uncorrected QT interval
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fredericia
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SCST	Sex cord-stromal tumor
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase

Abbreviation or specialist term	Explanation
SGPT	Serum glutamic-pyruvic transaminase
SMAD	Mothers against decapentaplegic homolog
SoA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reactions
TdP	Torsades de Pointes
TEAE	Treatment Emergent Adverse Event
TGF-β	Transforming growth factor-β
TKI	Tyrosine kinase inhibitors
TNF-R1	Tumor Necrosis Factor R1
TRAIL R1	Tumor Necrosis Factor – Related Apoptosis-Inducing Ligand R1
ULN	Upper Limit of Normal
US	United States
WNT4	Wingless/integrated Family Member 4
WOCBP	Woman of Childbearing Potential

4. INTRODUCTION

SpringWorks Therapeutics is developing nirogacestat which is a potent, small molecule, selective, reversible, non-competitive inhibitor of γ-secretase (GS) for the treatment of desmoid tumors (DT). The rationale for developing a GS inhibitor in cancer is supported by emerging evidence that Notch signaling, activated by GS cleavage, can drive the growth of a wide range of tumors.

4.1. STUDY RATIONALE

The purpose of this phase 2, single-arm study is to assess the anti-tumor activity of nirogacestat in adult participants with relapsed/refractory ovarian granulosa cell tumors (OvGCTs). In ongoing clinical trials for desmoid tumors, effects on ovarian function have been reported for female participants receiving nirogacestat. High levels of Follicle-stimulating hormone (FSH) not typical in pre-menopausal women have been detected in this study and are consistent with pituitary response to decreased sex steroid production.

These effects appear to be the result of NOTCH inhibition in human ovaries by nirogacestat. Further support for this suggested mechanism was seen in pre-clinical mouse models. These models show that the Notch signaling pathway, particularly the NOTCH 2 protein, is important in the differentiation and proliferation of ovarian granulosa cells (Zhang et al. 2011; Prasasya and Mayo 2018). The results from the clinical trials for desmoid tumors, strongly support that nirogacestat is capable of inhibiting NOTCH function in the growth of desmoid tumors the mechanism of which should translate to the development and growth of OvGCTs.

Standard of care treatment for relapsed/refractory OvGCT is platinum-based chemotherapy consisting of bleomycin, etoposide, and cisplatin or carboplatin and paclitaxel. These chemotherapy regimens, however, are not associated with durable remissions and most patients eventually develop progressive disease (PD) necessitating treatment with experimental agents. In prior studies in progressive OvGCTs, experimental agents have shown promise with only modest performance. In the Gynecologic Oncology Group (GOG) study of bevacizumab monotherapy, the Objective Response Rate (ORR) was 16.7% with a median Progression Free Survival (PFS) of 9.3 months (Brown et al. 2014). Combination therapy of bevacizumab with paclitaxel showed an improved ORR of 44% compared to 25% for paclitaxel monotherapy but did not improve PFS (Ray-Coquard et al. 2020).

Our hypothesis is that treatment of relapsed/refractory OvGCT with nirogacestat 150 mg twice daily (BID) will provide at least ORR of 30% with a secondary objective of improved duration of PFS and Overall Survival (OS) compared to bevacizumab monotherapy. Refer to Table 4 for study Objectives and Endpoints.

4.2. BACKGROUND

Granulosa cell tumors (GCT) of the ovary belong to the ovarian sex cord-stromal tumors (SCSTs), a group of benign and malignant neoplasms that develop from the sex cord (e.g., granulosa cell tumors, Sertoli cell tumors) or stromal cells (e.g., Leydig cell tumors, fibromas) or

both. Granulosa cell tumors are the most common type of malignant ovarian SCSTs comprising 90% of malignant SCSTs and 2 to 5 percent of all ovarian malignant neoplasms (Quirk and Natarajan 2005; Young 2005). Granulosa cell tumors of the ovary are divided into adult and juvenile types based on different clinical and histopathologic features (Schumer and Cannistra 2003). The juvenile type represents only 5% of cases and usually occurs in prepubertal girls and women younger than 30 years (Young 2005; Powell et al. 1993). The adult type most commonly presents during the perimenopausal or early postmenopausal period, with a median age of diagnosis between 50 and 54 years (Dridi et al. 2018; Kottarathil et al. 2013). There are no widely accepted clinically defined risk factors for this disease. Importantly, unlike epithelial ovarian cancer, there seems to be no known inherited predisposition for the development of these tumors, i.e. no association with germline mutations in BRCA1 and BRCA2 genes and no association with germline mutations in mismatch repair genes (Schumer and Cannistra 2003; Färkkilä et al. 2017).

Abdominal pain and abnormal uterine bleeding are the most common presenting symptoms (Koukourakis et al. 2008). Abdominal pain is related to the fact that GCTs can be hemorrhagic and large. Given its highly vascular nature, GCTs may occasionally present with hemorrhagic rupture of the tumor into the abdominal cavity and development of hemoperitoneum (Schumer and Cannistra 2003; Färkkilä et al. 2017; W.-L. Lee et al. 1999). Postmenopausal bleeding is due to prolonged exposure of the endometrium to tumor-derived estradiol, resulting in endometrial hyperplasia or endometrial adenocarcinoma. In premenopausal women, menstrual irregularity, menorrhagia, or even secondary amenorrhea may be the initial manifestation, while rarely, infertility (possibly due to increased inhibin secretion) may be the initial manifestation (Dridi et al. 2018; Segal, DePetrillo, and Thomas 1995). In premenarchal girls, isosexual precocious pseudo-puberty may be the initial presentation (Levin et al. 2018).

Microscopically, GCTs consist of small, round or oval granulosa cells with characteristic “coffee-bean” nuclei (Young 2005; King et al. 1996). Call-Exner bodies are characteristic of granulosa cell tumors and appear in 30% to 60% of cases; these constitute small cystic areas of fluid and cellular debris surrounded by well-differentiated granulosa cells (Young 2005; Ranganath R. et al. 2008). Call-Exner bodies and coffee-bean grooved nuclei are infrequent in the juvenile type of granulosa cell tumors (Powell et al. 1993; Ranganath R. et al. 2008).

Granulosa cell tumors are hormonally active and therefore several tumor markers have been used for postoperative surveillance and evaluation of response to therapy. Although estradiol may be helpful in monitoring the status of some patients, it is not a reliable marker because of a lack of consistent correlation between estradiol levels and tumor burden as well as disease progression; of note, absence of estradiol secretion is observed in approximately 30% of patients (Schumer and Cannistra 2003; Lappöhn et al. 1989). Inhibin is a more reliable marker of disease activity than estradiol and can serve as a useful marker of GCT activity in both pre- and postmenopausal women (Lappöhn et al. 1989). The alpha subunit of inhibin may associate with one of two distinct beta subunits, leading to the formation of either inhibin A or inhibin B. Although both inhibins may serve as tumor markers and should both be evaluated, inhibin B is more frequently elevated in patients with this disease (Robertson et al. 1999). Anti-müllerian

hormone (AMH), also referred to as Müllerian inhibitory substance (MIS) is another tumor marker for GCTs in postmenopausal and post-oophorectomy women (Färkkilä et al. 2017; Long et al. 2000). AMH is produced by the granulosa cells in the developing follicles of the ovary and AMH levels are elevated in a cyclical fashion throughout reproductive life but become undetectable in the postmenopausal period (Long et al. 2000).

Molecularly, the pathognomonic somatic missense point mutation 402C->G (C134W) in FOXL2 has been identified in 97% of adult subtype GCTs but only in 1 of 10 juvenile granulosa cell tumors (Shah et al. 2009). FOXL2 encodes a transcription factor that is expressed as a nuclear protein and is critically important in the development of granulosa cells. The FOXL2 C134W mutation leads to increased proliferation and survival of granulosa cells, and promotes hormonal changes (Färkkilä et al. 2017; Jamieson and Fuller 2012). The exact mechanism of how the FOXL2 mutation causes tumor formation is not completely understood. At the molecular level, the C134W mutation is not linked to alterations in the protein structure, but instead causes a change in the posttranslational modification (ubiquitination) leading to impaired interactions of FOXL2 with other transcription factors leading to subtle changes in the transcription of target genes (Färkkilä et al. 2017; Jamieson and Fuller 2012).

The staging system for GCTs is generally the same International Federation of Gynecology and Obstetrics (FIGO) staging used for epithelial ovarian cancer (Prat 2015). Surgery is the cornerstone of initial management for patients with GCTs (Schumer and Cannistra 2003; Powell et al. 1993; Segal, DePetrillo, and Thomas 1995; Peiretti et al. 2020). Surgery is necessary to establish a definitive diagnosis, perform staging, and remove as much tumor as possible with surgical principles being essentially identical to those used in the management of epithelial ovarian cancer (Peiretti et al. 2020; Abu-Rustum et al. 2006; Kuru et al. 2017; Ottolina et al. 2015; Stine, Pierce, and Soper 2014). Surgery typically includes total hysterectomy and bilateral salpingo-oophorectomy; conservation of a contralateral ovary and/or the uterus (if it has no evidence of disease) is reasonable in younger women with stage IA disease who wish to preserve fertility. This fertility-sparing approach recognizes the fact that GCTs are unilateral in more than 90% of cases. Surgery alone is acceptable treatment for patients with stage IA (Iyibozkurt et al. 2010). For those with stage IC and above, adjuvant chemotherapy is recommended, either the bleomycin, etoposide, plus cisplatin (BEP) regimen or the paclitaxel plus carboplatin regimen (Schumer and Cannistra 2003; Färkkilä et al. 2017; Iyibozkurt et al. 2010). For patients with stage IIA to IV disease or those with chemo-naïve disease, an ongoing randomized clinical trial (GOG264) is investigating carboplatin/paclitaxel vs BEP as the optimal first-line regimen in this disease (NCT01042522).

Treatment of recurrence involves surgery if the recurrent disease is resectable followed by postoperative platinum-based chemotherapy; postoperative radiation or observation can also be considered (Wolf et al. 1999; Hauspy et al. 2011). If disease is unresectable or the patients are not surgical candidates, platinum-based chemotherapy, endocrine therapy, and antiangiogenic therapy have shown activity in that setting. Chemotherapeutic regimens for recurrent disease may include BEP or carboplatin/paclitaxel depending on which regimen was used previously. However, no chemotherapy regimen is associated with durable remissions and the majority of

patients eventually experience progressive disease. Hormonal therapies such as luteinizing hormone-releasing hormone agonists (e.g., leuprolide), aromatase inhibitors, tamoxifen alone, progesterone alone, or a combination of tamoxifen and progesterone have been associated with long-term responses in some patients; however, most patients do not respond or exhibit brief responses (Hardy et al. 2005). Finally, antiangiogenic therapy with bevacizumab has shown promise; in a GOG phase II trial of bevacizumab in patients with metastatic SCSTs (89% were granulosa cell tumors) the objective response rate was 16.7% with stable disease in 77.8 percent of patients and a median progression-free survival of 9.3 months (Brown et al. 2014). Overall, there are currently no effective salvage therapies for patients with recurrent disease and, unlike epithelial ovarian cancer, there are currently no Food and Drug Administration (FDA) approved therapies, specific for granulosa cell tumors. Therefore, there is an urgent unmet need for novel therapies for granulosa cell tumors, especially targeted therapies based on a deeper understanding of the pathogenesis of these tumors and the role of the pathognomonic FOXL2 mutation.

4.3. BENEFIT/RISK ASSESSMENT

To date, the safety profile of single agent nirogacestat in participants with advanced cancer has been characterized by manageable and reversible toxicities. Currently, important identified risks related to nirogacestat include diarrhea, dermatologic reactions (maculopapular rash, hidradenitis, and folliculitis), ovarian dysfunction, electrolyte abnormalities (hypophosphatemia and hypokalaemia), and elevated liver transaminases. Important potential risks include embryofetal toxicity, effects on male fertility and in pediatric patients, epiphyseal disorder. The results of the nonclinical toxicology and safety pharmacology studies, together with the clinical experience in patients with advanced cancers, support the hypothesis that nirogacestat may represent an important therapeutic approach in patients with GCTs. Thus, the projected benefit/risk balance is considered favorable for further development in this patient population.

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

5. OBJECTIVES AND ENDPOINTS

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To determine the anti-tumor activity of nirogacestat in adult participants with relapsed/refractory OvGCT	Objective response rate (ORR) defined as the proportion of participants with Complete Response (CR) + Partial Response (PR) using RECIST v1.1 criteria
Secondary Objectives	**Secondary Endpoints**
To determine if nirogacestat delays progression or death in OvGCT	Estimate of proportion of participants who have not progressed or died at 6 months of follow-up: PFS-6. Progression is defined by RECIST v1.1
To describe overall survival in participants treated with nirogacestat	Estimate of 2-year overall survival, defined as the proportion of participants who have not died after 2 years of follow-up after their first dose of nirogacestat
To determine the effect of nirogacestat on ovarian cancer symptoms measured by Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI)	Change from baseline in FOSI
To determine the duration of response	Duration of response (DoR), defined as the time from first assessment of response (CR + PR using RECIST v1.1) to first disease progression defined by RECIST v1.1 or death, whichever comes first
To determine the pharmacokinetics (PK) of nirogacestat	Serum concentrations of nirogacestat will be measured to evaluate system exposures (C_{max}, C_{trough} and other PK parameters as data allow)
Safety Objectives	**Safety Endpoints**
To characterize the safety and tolerability of nirogacestat at a dose of 150 mg BID in adult participants with relapsed/refractory OvGCT	Key safety endpoints will include incidence of treatment emergent Adverse Events (TEAEs), changes in clinical laboratory parameters, vital signs, physician examination findings, and electrocardiograms (ECGs). Tolerability will be assessed according to toxicities graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Exploratory Objectives	**Exploratory Endpoints**
To detect FOXL2 C134W mutation as well as other genomic alterations and correlate these with response	Evaluate NGS status in baseline tumor tissue
To detect NICD and candidate biomarkers of response, and to correlate nirogacestat exposure with response	Evaluate change from Baseline: • Inhibin A&B, Follicle-stimulating hormone (FSH), estradiol, CA-125 and Müllerian Inhibiting Substance (MIS) / AMH • Circulating tumor DNA (ctDNA) Baseline NICD expression in tumor tissue

To describe progression free survival on continued nirogacestat treatment post first disease progression	Progression free survival on prolonged nirogacestat treatment, defined as time from first disease progression per RECIST v1.1 to second disease progression on continued nirogacestat treatment confirmed by investigator discretion or death, whichever comes first
To describe progression free survival on subsequent line of anticancer treatment	Progression free survival 2 (PFS2), defined as time from first dose of nirogacestat to second disease progression on subsequent line of anticancer treatment (after nirogacestat) confirmed by investigator discretion at long term safety follow-up visit or death, whichever comes first

6. STUDY DESIGN

6.1. OVERALL DESIGN

This is a multi-center, single-arm, Phase 2 open label treatment study to determine the efficacy, safety, tolerability, and pharmacokinetics of nirogacestat in adult participants with relapsed/refractory OvGCT. Approximately 43 eligible participants will be enrolled. Participants must have received at least one prior course of systemic therapy for OvGCT and have measurable disease per RECIST v1.1 to meet eligibility criteria.

Participants will be screened up to 28 days prior to the first dose of study treatment (nirogacestat) and full eligibility will be based on inclusion and exclusion criteria (Sections 7.1 and 7.2). At Cycle 1 Day 1 (C1D1), eligible participants will enroll in the study using the Interactive Response Technology (IRT) system and will orally administer their first dose of study treatment (150 mg; nirogacestat) followed by a 1-hour observation period. Following C1D1, participants will orally administer 150 mg of study treatment twice daily (BID), continuously in 28-day cycles. Participants will return to the clinic for study visits monthly for the first year (C1-C13) and then every 3 months thereafter (C16 and On).

Participants will remain on study treatment until death, disease progression (unless the participants meet criteria for continued treatment as defined in Section 9) discontinuation of study treatment for any reason, the study is stopped by the Sponsor for any reason, or participant qualifies for Sponsor's Compassionate Use program (see Section 9 for full discontinuation criteria).

Participants who discontinue study treatment early for any reason should return to the clinic for an End of Treatment (EOT) visit within 7 days after the Investigator determines study treatment will no longer be used and then again for a safety Follow-up (FUP) visit 30 days (+7 days) after the last does of study treatment.

The estimated study duration is 3 years, and all participants will be followed for at least 2 years (unless the study is prematurely stopped due to futility).

This study will use a Bayesian predictive probability approach with early stopping guidelines based on objective tumor response rate (CR+PR) intended to limit the accrual of participants to ineffective treatments. There will be no pause in accrual for interim assessments.

After accrual of full sample size, estimated ORR will be calculated after the last participant completes 6 cycles of therapy and has re-imaging at C7D1.

Refer to the Schedule of Assessments (SoA) (Section 1.3) for details on assessments and timing of study visits.

Refer to Section 1.2 for the study schema.

6.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study will look for direct evidence of anti-tumor activity of nirogacestat in a slow growing tumor by assessment of ORR and PFS-6. Previously studied agents in granulosa cell tumors have shown activity by increasing ORR and the proportion of PFS-6 (Brown et al. 2014; Ray-Coquard et al. 2020). As almost all participants with recurrence have measurable disease, ORR is a quantifiable metric to follow. Without an approved standard of care for relapsed disease, a single arm study is considered appropriate to define anti-tumor activity and tolerability in this population. This is consistent with the statements of the Fifth Ovarian Cancer Consensus Congress, where it was determined that innovative study designs may be required to offset small patient numbers (Leary et al. 2017).

The aim of this study is to determine if nirogacestat is an effective therapy for relapsed/refractory OvGCT. ORR using RECIST v1.1 will be used as the primary endpoint as ORR establishes a clinically relevant decision criterion for efficacy of the treatment in these patients. Secondary endpoints include PFS-6, duration of response, change from baseline FOSI, and OS. As an exploratory aim, tumor response assessments by RECIST v1.1 will be compared to serum tumor marker levels of CA-125, Inhibin A and Inhibin B, and AMH/MIS for response correlation.

Interim evaluations of ORR can be used as a criterion for determining whether the therapy is effective and worthy of continuation to full accrual thereby ruling out truly inactive agents for further investigation. A systemic review of prior studies in recurrent epithelial ovarian cancer have shown ORR as a possible surrogate for OS and PFS (Siddiqui et al. 2017). In this review, they determine that for every 10% increase in ORR, OS will increase by 2.83 months (Siddiqui et al. 2017). A secondary endpoint of two-year overall survival was based on overall survival in the ALIENOR/ENGOT-ov7 clinical trial where paclitaxel monotherapy showed a one and two year OS of 94% and 87% respectively and combination therapy of paclitaxel and bevacizumab resulted in one and two year OS of 93% and 73% respectively . Additionally, other non-study related factors such as prior therapy modalities, late effects of these treatments, and other underlying medical conditions may confound the PFS and OS of participants receiving study therapy justifying ORR as the metric of choice for analysis. Nirogacestat may also exhibit delayed anti-cancer responses. In this regard, the response patterns seen with such therapy may extend beyond the typical time course of responses seen with chemotherapeutic agents and, may manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Therefore, participants are allowed to remain on treatment after disease progression if they meet criteria for continued treatment as defined in Section 9.

To limit accrual of participants to ineffective treatments, the study will use a Bayesian strategy (J. Lee and Liu 2008; Chen et al. 2019) for continuous futility monitoring for early stopping based on ORR. Bayesian predictive probability will be used throughout the trial to assess the posterior probability of obtaining an ORR of no less than 15%.

6.3. JUSTIFICATION FOR DOSE

An open-label, non-randomized, Phase I dose finding study (Messersmith et al. 2015) in participants with advanced solid tumors was conducted to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for future clinical development of nirogacestat. In the dose-finding portion of the study, the MTD of nirogacestat administered BID continuously for 21 days was established at 220 mg BID. Additional participants were subsequently enrolled in the expansion cohort at 150 mg or 220 mg BID. The RP2D in participants with advanced solid tumors was determined to be 150 mg BID by comparing the tolerability, PK, and pharmacodynamic profile of nirogacestat at these 2 doses. At a dose level of 150 mg BID, the most frequently reported AEs were diarrhea (70%), fatigue (44%), nausea (39%), decreased appetite (26%), vomiting (26%), and hypophosphatemia (22%). HES4, a target gene of Notch, measured in peripheral blood samples showed the most consistent pharmacodynamic response, with a greater than 2-fold reduction observed in 17 of 19 evaluable participants with solid tumors. Nirogacestat was also investigated as a single agent in a Phase 2 study in 19 participants with triple-negative breast cancer at the RP2D of 150 mg BID. Neither efficacy nor PK were summarized for this study, but the AE profile was consistent with the Phase 1 study. Lastly and importantly, nirogacestat at 150 mg BID was studied in another Phase 2 study conducted by the National Cancer Institute in participants with progressing desmoid tumors (Kummar et al. 2017). In this study, nirogacestat activity was established with 5 PR (29%) out of 16 evaluable participants. On the basis of the dose-finding Phase I study and the activity in the desmoid tumor Phase 2, the 150 mg BID dose is currently being utilized in the ongoing randomized, double-blinded phase 3 study, Nirogacestat for Adults With Desmoid Tumor/Aggressive Fibromatosis (DT/AF) (DeFi) (ClinicalTrials.gov Identifier: NCT03785964).

6.4. END OF STUDY DEFINITION

The end of study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3) has been completed for the last participant in the study globally.

7. STUDY POPULATION

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

7.1. INCLUSION CRITERIA

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

Age

1. Participant must be aged ≥ 18 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participant has histologically confirmed recurrent adult-type granulosa cell tumor of the ovary prior to first dose of study treatment and agrees to provide archival or fresh tumor tissue.
3. Participant must have documented radiological evidence of relapse after at least one systemic therapy that is not amenable to surgery, or radiation and have measurable disease by RECIST v1.1 criteria (see Appendix 3). Prior systemic therapy is not limited to therapy type nor is any specific prior line of therapy required.
4. Participant must have a ECOG performance Grade of 0, 1, or 2 at Screening.
5. Participant must have adequate bone marrow, renal and hepatic function as defined by the following Screening laboratory values:
    a. Absolute neutrophil count (ANC) ≥1,000 cells/µL;
    b. Platelets ≥ 75,000/µL;
    c. Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Grade ≤ 1). Appendix A4-5)
    d. Total bilirubin ≤ 1.5 ×ULN (isolated total bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35% of total);
    e. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase) ≤ 2 x ULN; and
    f. Alkaline phosphatase < 2.5 × ULN.
6. Participant can swallow tablets (delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed).

Sex

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

a. Is not of childbearing potential (WOCBP);

OR

b. Is of childbearing potential but is abstinent or using 1 highly effective contraceptive method, as described in Appendix 6 during the treatment period and for at least 1 week after the last dose of study treatment. A second method of contraception is

required if the participant is using hormonal contraception, as coadministration with nirogacestat may alter the plasma concentrations of hormonal contraceptives resulting in reduced efficacy.

- Additionally, the participant agrees not to harvest or donate eggs (ova, oocytes) for the purpose of reproduction during the treatment period and for at least 1 week after the last dose of study treatment. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative serum pregnancy test result at Screening and a negative urine pregnancy test result at Baseline (C1D1) prior to the first dose of study treatment.
- Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Participant is capable of giving signed informed consent as described in Appendix A1-3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Participants who cannot read or understand the ICF and do not have a legally authorized representative may not be enrolled in the study.

7.2. EXCLUSION CRITERIA

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

Medical Conditions

1. Participant has any of the following:
    - Signs of bowel obstruction who require parenteral nutrition.
    - Malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of nirogacestat (e.g., gastric bypass, lap band, or other gastric procedures that would alter absorption).
2. Participant has experienced any of the following within 6 months of signing informed consent:
    - Clinically significant cardiac disease (New York Heart Association Class III or IV);
    - Myocardial infarction;
    - Severe/unstable angina;
    - Coronary/peripheral artery bypass graft;

- Symptomatic congestive heart failure;
- Cerebrovascular accident;
- Transient ischemic attack; or
- Symptomatic pulmonary embolism.

3. Participant has abnormal QT interval corrected by Fridericia's formula (> 470 msec for female participants, or > 480 msec for participants with bundle branch block) after electrolytes have been corrected at Screening.
4. Participant has congenital or acquired long QT syndrome or a history of additional risk factors for Torsades de Pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
5. Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones).
6. Participant has had a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to the first dose of study treatment.
7. Participant has a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last 5 years. Participants are also excluded if their previous cancer treatment contraindicates this protocol therapy.
8. Participant has CTCAE v5.0 Grade > 1 toxicity from prior therapy (except alopecia, anorexia or CTCAE grade 2 peripheral neuropathy).
9. Palliative radiotherapy with a limited field of radiation within 14 days or with wide field of radiation or to more than 30% of bone marrow within 28 days prior to the first dose of study treatment.

Prior/Concomitant Therapy

10. Participant previously received or is currently receiving therapy with GS inhibitors (i.e., nirogacestat) or anti-Notch antibody therapy.
11. Previous or current treatment for OvGCT:
    a. Participant previously received or is currently receiving bevacizumab (or other monoclonal antibody therapy with targeted anti-angiogenic activity) for OvGCT within 28 days (or 5 half-lives, whichever is shorter) prior to the first dose of study treatment; or
    b. Participant has received the following treatment types for OvGCT within 28 days (or 5 half-lives, whichever is longer) prior to the first dose of study treatment:
        - hormonal therapy;

- chemotherapy;
- immunotherapy;
- targeted therapy (e.g., tyrosine kinase inhibitors [TKIs], small molecule inhibitors); or
- any other investigational treatment

12. Participant is currently using or anticipates using food or drugs that are known strong/moderate cytochrome P450 3A4 (CYP3A4) inhibitors, or strong CYP3A inducers within 14 days prior to the first dose of study treatment.
13. Participant is using concomitant medications that are known to prolong the QT/QTcF interval including Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) antiarrhythmics at the time of informed consent. Non-antiarrhythmic medications which may prolong the QT/QTcF interval are allowed provided the participant does not have additional risk factors for Torsades de Pointes (TdP).

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

15. Participant with active infection requiring parenteral antibiotics at the time of signing the informed consent and during the screening period.
16. Participant has experienced other severe acute or chronic medical or psychiatric conditions, including recent (within 1 year of signing informed consent) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the participant inappropriate for entry into this study.
17. Participant has known hypersensitivity to the active substance or to any of the excipients of nirogacestat (Table 5).
18. Participant is unable to comply with study related procedures, has any intercurrent disease that is likely to prevent participant compliance with therapy or follow up as described in the protocol, or whose circumstances do not permit completion of the study or the required follow-up.

7.3. LIFESTYLE CONSIDERATIONS

- No specific lifestyle restrictions are required in this study.

- Study treatment may be taken without regard to food.
- Refer to Section 8.3 for more detail on concomitant therapy including exclusions and restrictions.

7.3.1. Meals and Dietary Restrictions

To avoid CYP3A4 inhibition, participants must refrain from consuming Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, or grapefruit hybrids at least 14 days prior to the first dose of study treatment and throughout the treatment period.

7.4. SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but do not receive study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (e.g., eligibility requirements failed), and any Serious Adverse Events (SAEs).

Individuals who do not meet the criteria for participation for the study (screen failures) may be rescreened at any time if provided the participant has not screen failed on any of the following Exclusion Criteria: #1, 4, 5, 10, or 17.

Participants do not need to wait the full 28 days of the screening period to rescreen. There is no set limit to how many times a participant may be rescreened if the Investigator considers the rescreening medically and scientifically appropriate, and the screening assessments continue to tolerate for the participant. Rescreened participants must be re-consented and will be assigned a new participant number at the time of rescreening.

8. STUDY TREATMENT

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

8.1. STUDY TREATMENT ADMINISTERED

- Participants will be instructed to swallow tablets whole and not to chew them prior to swallowing.
- No tablet should be ingested if it is broken, cracked, or otherwise compromised (e.g., not fully intact).
- Participants should take their dose BID orally, approximately every 12 hours, without regard to food.
- Participants will be instructed to record their daily administration of each study treatment dose in a Dosing Diary.

- If a participant misses a scheduled dose of study treatment, and it is within 6 hours of the scheduled dose, the participant should immediately administer the missed dose and resume study treatment in accordance with the normal administration schedule. If more than 6 hours have elapsed since the time of scheduled administration, the participant should be instructed not to administer the missed dose and to resume study treatment as prescribed.
- Participants should not take 2 doses together to "make up" for a missed dose.
- If a participant vomits any time after taking a dose, then they must be instructed not to take another dose to "make up" for vomiting, but rather to resume subsequent doses as prescribed.
- If a participant inadvertently takes 1 extra dose, then the participant should not take the next scheduled dose of study treatment.
- Delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.

Table 5: Study Treatment Administered

Study treatment name	Nirogacestat
Dosage formulation	Tablet
Unit dose strength(s)	50 mg
Dosage level(s)	150 mg BID
Route of administration	Oral
Sourcing	Sponsor will provide Sites with study treatment for individual participant distribution
Packaging and labeling	Study treatment will be provided in 90 count bottles. Each bottle will be labeled as required per country requirement
Former Name	PF-03084014
Ingredients	Opadry® QX Film Coated Tablets: Nirogacestat; Microcrystalline Cellulose; Lactose Monohydrate; Sodium Starch Glycolate; Magnesium Stearate; Macrogol (Polyethylene glycol) Polyvinyl Alcohol Graft Copolymer: Talc; Titanium Dioxide; Glyceryl Monocaprylocaprate Type 1; Polyvinyl Alcohol – Part Hydrolyzed; Yellow #6 / Sunset Yellow FCF Aluminum Lake; Iron Oxide Yellow

8.1.1. Dosing Administration

Participants will administer 150 mg (3 × 50 mg tablets) of study treatment BID (approximately every 12 hours, without regard to food), continuously in 28-day cycles.

8.1.2. Preparation/Handling/Storage/Accountability

Study treatment will be dispensed to participants during scheduled study visits every cycle during the first year and then every 3 cycles thereafter, as described in the SoA (Section 1.3) or unscheduled visits if study treatment is damaged/lost or a dose modification (Section 8.4) is necessary.

Participants will be instructed to keep their study treatment in the bottles provided and not transfer it to any other containers.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. Study treatment should be dispensed at the study site; however, Direct-to Patient (DTP) shipping may be allowed with advance approval from the Sponsor in the event of a public health crisis such as COVID-19. Direct-To-Patient shipping is not allowed at the C1D1 study visit.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatments are provided in the pharmacy manual.

8.2. STUDY TREATMENT COMPLIANCE

Participant compliance with study treatment will be monitored throughout the study. At each applicable study visit (Section 1.3) the participant should be asked whether they have been compliant with dosing instructions. Compliance will also be assessed by counting returned tablets at the applicable study visits. Any discrepancies will be discussed with the participant and will be recorded in the source documentation.

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

In the case of an overdose, refer to Section 11.4 for instructions.

8.3. CONCOMITANT THERAPY

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

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.3.1. Known Drug Interactions

8.3.1.1. Cytochrome P450 Inhibitors and Inducers

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

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

8.3.1.2. Cytochrome 3A4 Substrates

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

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

8.3.1.3. Anti-Emetic and Anti-Diarrheal Therapy

The choice of anti-emetic drug(s) and anti-diarrheal drug(s), as well as the duration of treatment, is at the discretion of the Investigator assuming there is no known or expected drug-drug interaction (DDI). If a DDI is expected, then the drug(s) use must be approved by the Medical Monitor.

8.3.1.4. Other Concomitant Therapy

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

The effect of nirogacestat on the exposure of hormonal contraceptives has not been evaluated. However, induction of these cytochrome P450 enzymes has been associated with reduced plasma exposure of various hormonal contraceptives resulting in reduced efficacy.

Nonclinical studies have indicated that nirogacestat is a substrate for the drug efflux transporter P-glycoprotein (P-gp). Therefore, caution should be used when co-administering the study treatment with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, elacridar, felodipine, mibefradil, nitrendipine, quinidine, ranolazine, talinolol, and valspodar.

Co-administration of gastric Acid Reducing Agents (ARAs) such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, etc.) may reduce the absorption of nirogacestat. These drugs should be avoided if possible or, when necessary, administered 4 hours following the dose of study treatment. Twice daily administration of ARAs is not allowed during the treatment period.

Administration of potential QTC prolonging medications aside from anti-arrhythmics as listed below, should be used with caution due to possibility of additive QTC prolongation with nirogacestat (See Appendix A4-4).

8.3.2. Excluded/Restricted Concomitant Medications and/or Procedures

Table 6 describes the concomitant medications and/or procedures that are excluded/restricted prior and/or throughout the duration of the study until the termination of study treatment. Contact the Medical Monitor with any questions regarding excluded/restricted medications.

Table 6: Excluded/Restricted Medications and/or Procedures

Medication/Procedure	Exclusion/Restriction
• Hormonal therapy, chemotherapy, immunotherapy, targeted therapy (e.g., TKIs, small molecule inhibitors) • Any other investigational treatment for OvGCT.	• Not allowed within 28 days (or 5 half-lives, whichever is longer) prior to first dose of study treatment; and • Not allowed throughout the duration of the treatment period.
• Bevacizumab (or other monoclonal antibody therapy with targeted anti-angiogenic activity)	• Not allowed within 28 days (or 5 half-lives, whichever is shorter) prior to first dose of study treatment; and • Not allowed throughout the duration of the treatment period.
• Strong/moderate CYP3A4 inhibitors; and • Strong/moderate CYP3A4 inducers.	• Not allowed within 14 days prior to first dose of study treatment. • Not allowed throughout the duration of the treatment period.
• CY3A4 substrates with a narrow therapeutic index.	• Should be avoided if possible; and • If co-administration is unavoidable, the participant should be monitored closely for toxicity and investigator should consider reducing or titrating the dose of the substrate as necessary.
• Gastric ARAs such as proton pump inhibitors.	• Should be avoided if a reasonable alternative is available; and • If administration is necessary, should be administered 4 hours after the dose of study treatment. • Twice daily administration of ARAs is not allowed during the treatment period.
• GS inhibitors; • Anti-Notch antibody therapy; and • Gastric bypass, lap band, or other gastric procedures that would alter absorption.	• No prior use, therapy or procedure is allowed; and • Not allowed throughout the duration of the treatment period.
• Major surgical procedure or excisional biopsy.	• Not allowed within 28 days prior to first dose of study treatment.
• Antiarrhythmic medications that are known to prolong the QT/QTcF interval including: Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) antiarrhythmics; • Potentially curative radiotherapy.	• Not allowed within 28 days prior to first dose of study treatment; and • Not allowed throughout the duration of the treatment period.

Medication/Procedure	Exclusion/Restriction
• Delivery of nirogacestat via nasogastric tube or gastrostomy tube.	• Not allowed throughout the duration of the treatment period.
• Enrollment in another clinical study with any investigational drug or device.[1]	• Not allowed within 28 days prior to first dose of study treatment; and • Not allowed throughout the duration of the treatment period.

CYP3A4 = Cytochrome P450 3A4; GS = Gamma-secretase; QT = Uncorrected QT interval; QTcF = Corrected QT interval by Fridericia

[1]Participation in an observational study may be allowed on a case-by-case basis with prior Medical Monitor approval.

8.3.3. Supportive Care

8.3.3.1. Phosphate Supplements

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

8.3.3.2. Palliative Care

Systemic or local therapy to the Granulosa cell tumors is not permitted.

Medications for the standard management of symptoms or supportive care for the side effects of study treatment may be administered at the investigator's discretion; unless they are excluded concomitant medications (Section 8.3.2).

Palliative radiation therapy may be permitted after consultation with the Medical Monitor. Radiation will be limited to non-target lesions only and will be documented in the eCRF.

Thus, the following therapies are not permitted during the study:

- Other anti-neoplastic therapy, including cytotoxic agents, small molecule inhibitors, targeted agents, endocrine therapy or other antibodies;
- Potentially curative radiotherapy;
- Surgical resection of granulosa cell tumors; and
- Any other investigational therapy.

8.4. DOSE MODIFICATION

Every effort will be made to administer study treatment (nirogacestat) at 150 mg BID. However, dosing will be interrupted and/or dose reduced for the AEs described in Table 7. Study treatment may also be modified to manage other AEs in collaboration with the Medical Monitor.

If an event listed in Table 7 has an alternative etiology and is not considered study treatment related, dose modifications may not be required; consult with the Medical Monitor.

If a participant experiences an AE as described in Table 7, hold study treatment until the AE is resolved to ≤ Grade 1 or baseline.

- If the AE is resolved within 14 days, then study treatment should be restarted at the reduced dose as described in Table 7.
- If the AE does not resolve to ≤ Grade 1 or baseline after holding study treatment for 22 days, study treatment may be resumed only after discussion with the Medical Monitor.

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

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

Table 7: Dose Modifications or Interruptions for Selected Toxicities

Toxicity (NCI CTCAE v5.0)[1]	Intervention
Gastrointestinal Toxicities	
Grade ≥ 3 diarrhea persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Grade ≥ 3 nausea persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Grade ≥ 3 vomiting persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Other toxicities	
Grade ≥ 3 skin toxicity	Decrease dose to 100 mg BID
Grade ≥ 3 hypophosphatemia persisting for ≥ 7 days despite maximal replacement therapy and in the absence of symptoms	Decrease dose to 100 mg BID
Any clinically significant Grade ≥ 3 toxicities	Decrease dose to 100 mg BID
Anaphylaxis	Permanently discontinue
Grade ≥ 3 hypersensitivity reaction	Permanently discontinue
Hepatic toxicities	Refer to Section 9.1.1

NCI = National Cancer Institute; CTCAE = Common Terminology Criteria for Adverse Events.
[1]Refer to the study reference manual for details on managing AEs.

9. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

It may be necessary for a participant to permanently discontinue study treatment (nirogacestat) early. In this case, the participant will return to the site for an EOT visit and a post dose safety

follow-up (FUP) visit (refer to SoA; Section 1.3 for a complete list of required assessments to be conducted).

Reasons for discontinuation of study treatment at any time may include:

- Clinical (including physical examination) or radiographic (using RECIST v1.1) evidence of progressive disease (PD);
    - Treatment after Initial Evidence of Disease Progression
        - Study treatment may be continued at the investigator's discretion if the participant is clinically stable as defined by the following criteria:
            - Absence of clinical signs and symptoms of disease progression
            - No decline in ECOG performance status
            - Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.
        - The participant will be reassessed at the next protocol-defined CT or MRI scan for tumor measurement in order to rule out pseudo-progression.
            - If repeat imaging demonstrates CR, PR, or SD compared to the first scan that showed disease progression, treatment with study treatment may be continued.
            - If repeat imaging demonstrates PD, defined as ≥10% increase in tumor burden compared to the first scan that showed disease progression, participants should be discontinued from study treatment.
        - All decisions to continue study treatment beyond initial progression must be discussed with the Medical Monitors and documented in source documents.
- Adverse events requiring removal from protocol therapy as stated in Section 9.1. Any SAE (refer to Appendix A5-1.3 for SAE criteria), clinically significant AE (refer to QTcF stopping criteria, Section 9.1.2), severe laboratory abnormality (refer to liver chemistry stopping criteria, Section 9.1.1), any grade ≥ 3 hypersensitivity reaction, anaphylaxis, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the participant;
- The initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy, small molecule inhibitors, immunotherapy, or targeted therapy) for granulosa cell tumor;
- Participants who receive concurrent investigational therapy or anti-cancer therapy;
- Refusal of further protocol therapy by participant;
- Treating Physician determines it is the participant's best interest;

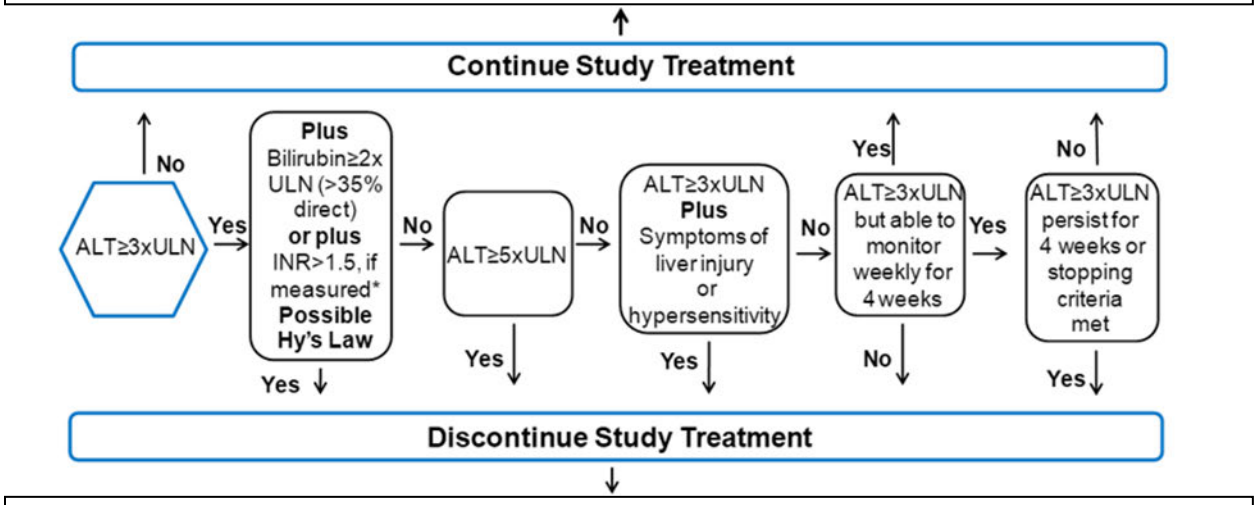
- Non-compliance: Participant failure to comply with protocol requirements or study-related procedures;
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the requirements of the protocol;
- Pregnancy (refer to Sections 9.1.3 and 11.3.6 for additional details);
- Requirement of prohibited concomitant medication or procedure (Section 8.3.2);
- Withdrawal of consent for any required observations or any further data submission;
- Termination of the study by the Sponsor or the regulatory authority.

9.1. DISCONTINUATION OF STUDY TREATMENT

9.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 2 or if the Investigator believes that it is in best interest of the participant.

Figure 2: Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



9.1.2. QTcF Stopping Criteria

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

A participant who meets either of the following bulleted criterion should be confirmed with triplicate ECGs. If these findings are confirmed based on the average of the triplicate readings, the participant will be withdrawn from the study treatment:

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

Table 8 describes the discontinuation criteria for participants with underlying bundle branch block.

Table 8: Bundle Branch Block Discontinuation Criteria

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

QTcF = QT interval corrected using Fridericia's formula; msec = millisecond

See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

9.1.3. Pregnancy

A participant who becomes pregnant will be withdrawn from study treatment. See Section 11.3.6 for additional details.

9.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, the EOT visit should be conducted. See SoA (Section 1.3) for specific data to be collected at the time of study discontinuation, as well as follow-up for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested. The Sponsor must be notified if the participant requests destruction of sample, and the Investigator must document this in the site study records.

9.3. LOST TO FOLLOW UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as whole is handled as part of Appendix A1-7.

10. DURATION OF STUDY

The study will continue until at least the date that the survival data needed for the estimate of 2-year overall survival is obtained, or the study is prematurely stopped due to futility.

11. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA is essential and required for study conduct.
- All screening evaluations must be completed using a Pre-Enrollment Review Form, which should be provided to the Medical Monitor at least two days prior to C1D1 for review to confirm that potential participants meet all eligibility criteria (Section 7.1 and

Section 7.2). The electronic data capture (EDC) will capture all participants who sign the ICF, including all screen-failures.

- The amount of blood collected from each participant will be approximately 350 mL each year during the study. This does not include any extra assessments that may be required for unscheduled assessments or EOT/FUP visits. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In the event that a study site or participant is unable to complete a study visit or procedure due to restrictions caused by a public health emergency such as COVID-19, the following accommodations may be allowed temporarily with prior approval from the Medical Monitor. Any deviations from the study protocol due to a public health emergency should be documented in the source data and electronic Case Report Form (eCRF) and reported to the IRB/IEC in accordance with their reporting requirements.
    - If a study participant cannot attend a study visit onsite due to a public health emergency, they may be able to attend a local hospital/clinic or arrange for a telehealth or home healthcare visit.
    - Clinical laboratory assessments (safety labs and pregnancy tests) may be performed locally with results and local laboratory normal values entered into the eCRF.
    - Electrocardiograms may be performed locally. If ECGs are performed locally, ECG tracings should be collected, and the Investigator (or designee) assessment should be documented.
    - Study imaging should be performed per the schedule in the SoA (Section 1.3); however, imaging may be performed at another imaging center (locally to the participant) with prior Medical Monitor approval.

11.1. EFFICACY ASSESSMENTS

11.1.1. Tumor Imaging

Tumor response will be assessed by CT or MRI (contrast required unless contraindicated). The same imaging modality and radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (i.e., the same contrast protocol for scans). Tumor response and progression of cancer under study in real time will be evaluated locally at each study site according to RECIST v1.1 (Eisenhauer 2009). See Appendix 3 RECIST Criteria response definitions. All RECIST measurements will be done by the site's local radiologist.

Chest imaging using CXR or CT (contrast not required) will also be required as described in the SoA and should be obtained per institutional standards.

Standard of care scan(s) acquired prior to the participant signing ICF may be used as the participant's screening visit scans if they were obtained within 28 days of the first dose of study treatment.

On treatment scans may be acquired (-) 7 days prior to the study visit or within the study visit window as described in the SoA (Section 1.3).

Imaging must be done prior to tumor biopsy if assessments occur on the same day.

Whenever disease progression is suspected (e.g., symptomatic deterioration) throughout the study, unscheduled scans may be acquired.

11.1.2. Other Objective Parameters

11.1.2.1. Patient-Reported Outcomes (PROs)

Patient-reported Outcomes (PROs) will be assessed at each clinic visit using the Functional Assessment of Cancer therapy Ovarian Cancer Symptom Index (FOSI). The FOSI is an 8-question evaluation scored on a Likert scale of 0-4 from not at all to very much. Metrics assessed include lack of energy, vomiting, pain, nausea, swelling in stomach area, concern condition will get worse, quality of life assessment and stomach cramps. When possible, the participant should complete the paper FOSI questionnaire as the first assessment during the applicable study visits (refer to the SoA; Section 1.3) to minimize bias. This assessment takes approximately 5 minutes to complete and is manually calculated to determine a symptom index score correlating with level of patient symptoms (Beaumont et al. 2007). Change from baseline in the FOSI score and individual responses will be scored at each applicable study visit, EOT, and the safety FUP.

11.2. SAFETY ASSESSMENTS

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

11.2.1. Demographics Data and Medical History

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

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (i.e., WOCBP or no WOCBP); history of alcohol or substance abuse and collection of concomitant medications.

The medical history should also include a detailed menstrual history including the date of the last menstrual cycle and any history of amenorrhea, menstrual irregularities, or infertility.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation.

11.2.2. Physical Examinations and Eastern Cooperative Oncology Group Performance (ECOG) Status

Physical examinations, as well as height/weight, and assessment of ECOG performance status (per Investigator's assessment) (Appendix A4-2) will be required throughout the study as described in the SoA. Height to be measured at Screening only; a historical height measured within 1 year prior to signing informed consent may be used as the screening height.

A physical examination should include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Neurological, Lymphatic, and Skin systems. A pelvic exam will also be required for participants whose disease can be evaluated by pelvic exam.

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

11.2.3. Vital Signs

Body temperature, heart rate, respiratory rate, and blood pressure will be assessed throughout the study as described in the SoA (Section 1.3).

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

Blood pressure, respiratory rate, heart rate and body temperature should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

Vital signs can be repeated per clinical judgement.

11.2.4. Electrocardiograms

Single 12-lead ECG will be obtained, and the following data parameters will be reported: HR, PR, QRS, QT, and QTcF intervals at the timepoints described in the SoA (Section 1.3). Prior to ECG assessments, participants should rest in a semi-recumbent supine position for at least 5 minutes. Refer to Section 9.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

For safety monitoring purposes, the Investigator (or appropriate delegated designee) must review and assess any abnormalities for clinical significance, and then sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the source documentation at the site.

Refer to Section 9.1.2 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

11.2.5. Clinical Safety Laboratory Assessments

See Appendix A4-1 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

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

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

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

11.2.6. Pregnancy Testing

Pregnancy testing will only be required for women of childbearing potential (WOCBP) (refer to Appendix 6 for definition of WOCBP and additional details on contraceptive guidelines and collection of pregnancy information).

A negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (prior to first dose of study treatment) will be required to meet study entry criteria.

Monthly urine pregnancy tests will be required for WOCBP at each study visit (refer to SoA; Section 1.3). Following C13D1, between study visits, participants will be required to return to the site for monthly (every 28 days [+/- 2 days]) urine pregnancy tests. If it is more convenient to the participant, they may alternatively visit a local laboratory that has been pre-approved by the Sponsor (or designee) for this assessment (refer to study reference manual for additional detail).

Serum pregnancy tests may be conducted in place of urine pregnancy tests throughout the study if required by local regulations.

11.2.7. Remote Monthly Wellness Checks

Remote monthly (every 28 days [+/- 2 days]) telephone or email contact is required following C13D1 until EOT. The wellness checks may be replaced by a face-to-face interaction when study visits occur provided the information can be obtained during the visit.

During these wellness checks, site staff should assess, at a minimum, AEs, changes to concomitant medications, and dosing compliance.

A copy of the telephone report or email must be documented in the source documentation. Email must not replace direct follow-up by phone or in-clinic visits for clinically significant AEs or

other emergent issues. Adverse events and concomitant medication changes will be captured in the associated eCRFs.

11.2.8. 2-Year Survival Check-In

Sites will document participant's survival status approximately 2 years after the participant's first dose of study treatment. If the participant discontinues from study treatment prior to the 2-year check-in, quarterly telephone or email contact following EOT is required until the 2-year survival data point has been collected. Additionally, collection of subsequent anticancer therapy after nirogacestat and overall response to this therapy will be recorded. Only information about the subsequent therapy used directly after nirogacestat is required along with the final survival outcome at the 2-year check point.

A copy of the telephone report or email must be documented in the source documentation and the survival data point will be captured in the eCRF.

11.3. ADVERSE EVENTS (AEs), ADVERSE EVENTS OF SPECIAL INTEREST (AESIs), SERIOUS ADVERSE EVENTS (SAEs), SPECIAL SITUATIONS, AND PREGNANCY

The definitions of an AE, SAE, AESI, Special Situations, Adverse Drug Reaction (ADR), Serious Adverse Reaction (SAR), and Suspected Unexpected Serious Adverse Reaction (SUSAR) can be found in Appendix 5.

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

The Investigator or any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE/AESI/SAE/Special Situation and remain responsible for following up on the events that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment.

11.3.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are selected non-serious and serious AEs that must be reported regardless of relationship to study treatment.

Refer to Table 9 for the AESIs identified for this study. AESIs will be followed until resolution or return to baseline.

Following medical evaluation, Sites may be contacted to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event. Please note this table lists known AESIs; additional events may be identified during the course of the study.

Table 9: Adverse Events of Special Interest (AESI)

Skin Rash (reported as AESI if clinically significant Grade 2 and all Grade ≥ 3. Per CTCAE v5.0)
Maculopapular rash
Pruritic rash
Erythematous rash
Folliculitis
Hidradenitis suppurativa
Elevated Liver Enzymes (reported as AESI if Grade ≥ 2, per CTCAE v5.0)
AST
ALT
Alkaline Phosphatase
Total bilirubin
Electrolyte Insufficiency (reported as AESI if Grade ≥ 3, per CTCAE v5.0)
Hypophosphatemia
Hypokalemia
Hypomagnesemia
Drug Reactions (reported as AESI for any grade)
Allergic reaction
Anaphylaxis
(Drug) hypersensitivity
Ovarian Toxicity[1] (reported as AESI for any grade)
Ovarian dysfunction
Ovarian disorder
Amenorrhea
Oligomenorrhea
Premature menopause
Ovarian failure
Skin Cancer (reported as AESI for any grade)
Basal cell carcinoma
Squamous cell carcinoma (of skin)
Keratoacanthoma
Actinic keratosis
Any other skin cancer

AESI = Adverse Event of Special Interest; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events

[1]Participants reporting AEs/AESIs/SAEs of ovarian toxicity will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).

11.3.2. Time Period and Frequency for Collecting Safety Event Information

- AEs/AESIs/SAEs/Special Situations will be collected from the signing of the ICF until 30 days after the last dose of study treatment.
- Pregnancies will be reported from the first dose of study treatment until 30 days after the last dose of study treatment. However, if a pregnancy is reported by the participant 30 days after the last dose of study treatment, the pregnancy should still be reported to Safety.
- Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify Safety.
- All AESIs/SAEs/Special Situations will be reported to the Sponsor's safety group (referred to as 'Safety' throughout this document) within the timeframes as described in Table 10.

Table 10: AESI/SAE/Special Situation Reporting Timeframes

Type of Safety Event	Reporting Timeframe to Safety
SAE	Initial SAE report: must be reported to Safety immediately and under no circumstances should exceed 24 hours of awareness. Follow-up SAE report: Investigator will submit any updated SAE data to Safety within 24 hours of it being available.
AESI	Serious AESIs: must be reported immediately and under no circumstance should this exceed 24 hours. Non-serious AESIs: must be reported to Safety as soon as possible, but no later than 5 business days of awareness.
Special Situation	If there is an associated SAE with the Special Situation, it must be reported immediately and under no circumstance should this exceed 24 hours. If there no associated SAE with the Special Situation, it must be reported to Safety as soon as possible, but no later than 5 business days of awareness.
Pregnancy	If a pregnancy is reported, the Investigator must inform Safety within 24 hours of learning of the pregnancy.

AESI = Adverse Event of Special Interest; SAE = Serious Adverse Event

11.3.3. Method of Detecting AEs/AESIs/SAEs/Special Situations

The method of recording, evaluating, and assessing causality of AEs/AESIs/SAEs/Special Situations, and the procedures for completing and transmitting reports are provided in Appendix A5-2.

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

11.3.4. Follow-up of AEs/AESIs/SAEs/Special Situations

After the initial AE/AESI/SAE/Special Situation report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Table 9), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 9.3).

Refer to Appendix 5 for additional details regarding recording and reporting follow-up information.

11.3.5. Regulatory Reporting Requirements for SAEs

Prompt notification (within 24 hours of learning of the event) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators and report per Sponsor procedures. SUSARs will be reported directly to regulatory authorities' databases, such as EudraVigilance, or per other method as determined by governing regulations.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements/Sponsor policy and forwarded to Investigators as necessary.

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

11.3.6. Pregnancy

If a pregnancy is reported, the Investigator must inform Safety within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

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

11.4. TREATMENT OF OVERDOSE

For this study, any dose of study treatment greater than a 450 mg daily dose of study treatment within a 24-hour time period be considered an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately (refer to Appendix 8 for contact information).
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 4 days.
3. Document the quantity of the excess dose as well as the duration of the overdose on the Special Circumstances eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

11.5. PHARMACOKINETICS

- The following pre- and post-dose PK samples will be collected during the study to allow for determination of the pharmacokinetics (PK) of nirogacestat and exploratory exposure-response analysis.

Visit	Timepoint
C2D1	Pre-dose (prior to morning dose of study treatment)
	Post-dose (1-hour after morning dose of study treatment)
C3D1	Pre-dose (prior to morning dose of study treatment)
C4D1	Pre-dose (prior to morning dose of study treatment)
C5D1	Pre-dose (prior to morning dose of study treatment)
C6D1	Pre-dose (prior to morning dose of study treatment)
C7D1	Pre-dose (prior to morning dose of study treatment)

- For pre-dose PK visits:
    - The evening before the study visit, participants will record the exact time study treatment was taken in the Dosing Diary.
    - On the day of the study visit, participants will not take their planned morning dose at home. The morning dose will be taken in the clinic following the pre-dose PK blood draw.
- For post-dose PK visit:
    - All efforts should be made to obtain the PK sample as close to the 1-hour timepoint following the onsite dose of study treatment. However, if the PK

time is captured in the source documents and eCRF, a protocol deviation will not be captured.

- Whole blood samples of approximately 4 mL each will be collected for measurement of serum concentrations of nirogacestat.
- Sites will document the exact date and time (24-hour clock time) each PK sample is taken in the source documents.
- Instructions for the collection, handling, and shipment of PK samples will be included in the central laboratory manual.

11.6. BIOMARKERS

Translational components of this study aim to detect the FOXL2 C134W mutation as well as other genomic alterations to correlate with response. Additionally, IHC will be used to assess baseline NICD expression to correlate expression levels as a predictive marker for treatment response. Archival Formalin-Fixed Paraffin-Embedded (FFPE) specimen (a block or 15-20 unstained slides) will need to be provided for targeted NGS at a central laboratory. If archival tissue is not available, a screening biopsy will be required. Refer to central lab manual for additional details.

Blood samples for circulating biomarkers (hormones, protein, DNA) will be collected and shipped to a central laboratory. Baseline and on-treatment samples will be collected to monitor levels in response to treatment.

- FSH, LH, Estradiol, and Progesterone will be assessed at Screening, Baseline, Day 1 of every cycle, EOT, and the 30-day follow-up visit
- Inhibin A, Inhibin B, AMH/MIS and CA-125 will be assessed at Baseline, Day 1 of every cycle, EOT, and the 30-day follow-up visit
- Circulating tumor DNA (ctDNA) will be assessed at Baseline, Cycle 3 Day 1, and EOT

Additional biomarkers may also be measured, based on emerging clinical and literature data pertaining to Notch biology. Full details regarding collection, processing, storage and shipping of all biomarker samples will be provided in the central laboratory manual.

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

12. STATISTICAL CONSIDERATIONS

12.1. STATISTICAL HYPOTHESES

The primary objective of the study is to estimate the objective response rate for participants receiving nirogacestat who have relapsed/refractory ovarian granulosa cell tumors and who have

measurable disease. Since this is a first-in-human proof of concept study for the indication, no formal hypothesis testing is contemplated.

12.2. SAMPLE SIZE AND DESIGN CHARACTERISTICS

A prior GOG phase 2 trial in previously treated participants with stromal tumors evaluated the efficacy and safety of bevacizumab monotherapy in participants with recurrent sex cord stromal tumors of the ovary. The ORR in this study was 16.7%. (Brown et al. 2014). Following this outcome, the ALIENOR/ENGOT ov7 trial randomized participants to see if the addition of bevacizumab to paclitaxel had effect on the PFS rate among participants with relapsed ovarian sex cord stromal tumors. While the combination therapy of paclitaxel and bevacizumab showed an ORR of 44% over paclitaxel monotherapy, the PFS remained equivocal between the two treatment groups (Ray-Coquard et al. 2020). Based on the ORR from the bevacizumab monotherapy trial, this study aims for an ORR of 30% with PFS as a secondary endpoint.

No formal sample size calculation is attempted. The initial goal of accrual for this study is 43 participants which should provide sufficient sample size for interim evaluations for futility with a Bayesian strategy of continuous monitoring. Participant accrual will not be paused during the interim evaluations. The Bayesian approach to be used for futility analysis assumes a beta-binomial distribution with an uninformative prior of beta distribution (J. Lee and Liu 2008; Chen et al. 2019). Assume at an assessment point, the study has accrued X responders out of n (≤43) participants. With a prior distribution of *beta (a, b), X* follows a binomial distribution and the posterior distribution of the response rate follows a beta distribution with parameters *(a+x, b+n-x)*, where x is the observed value of *X*. Thus, the number of responses in the potential *(43-n)* future participants, *Y*, follows a beta-binomial distribution with parameters *(43-n, a+x, b+n-x)*. From the observed responders x and a target ORR, the predictive probability of reaching the target ORR at the end of study can be calculated with the beta-binomial distribution. If the predictive probability is too low, e.g., ≤10%, the study may be terminated for futility. A high predictive probability, e.g., >85%, suggests high likelihood of achieving treatment efficacy at the end of the study.

For this study, we assume that a response rate of ≤15% at the end of study is considered ineffective for the treatment, and enrollment will stop if the posterior probability of ORR >15% is less than 0.1. On the other hand, the treatment is considered promising if the posterior probability of ORR >15% is higher than 0.85, that is, if the posterior distribution provides

$$Prob\{ORR > 0.15|data\} > 0.85.$$

For calculating the posterior probability, a prior of beta (0.1, 0.9) could be assumed. These parameters (0.1 and 0.9) of the beta prior correspond to the initial assumed distribution of ORR with mean equal to 0.1/(0.1+0.9) = 10% (that is, an initial belief of ORR around 10%). The beta parameters will be updated according to observed number of responders at each analysis.

Given the cutoff points of the predictive probability for futility and efficacy, the characteristics of the design can be assessed in terms of type I and II errors. For example, if the cutoff points are set at 10% for futility and 85% for efficacy, the above Bayesian rule will result in futility

stopping boundaries of 1, 2, and 5 or fewer respondents if interim evaluations were to occur at enrollment of 10, 20, 30 participants, respectively. If the true rate of ORR is 15%, the chance to conclude treatment efficacy at the end of the study is 7% (Type I error). However, the probability to stop the trial early is 79%. If the true rate of ORR is 30%, the chance to conclude treatment efficacy at the end of the study is 76%.

A set of simulations using a frequentist framework under the similar interim evaluation schedule as above are performed for comparisons. Specifically, the type I and II errors are simulated for scenarios where the study ceases for futility when the ORRs are 0%, ≤5%, ≤10%, or 15% when 10, 20, 30, and 43 participants have been enrolled, respectively. Those conditions correspond to stopping for futility when there are fewer than or equal to 0, 1, 3, and 6 respondents in the three interim and final analyses, respectively. Table 11 below provides results based on 10,000 simulations of probability of early stopping for futility and the expected overall sample sizes.

Table 11: Simulated Probability of Early Stopping under Assumed ORR

Interim Time Point (Enrollment at N =)		10	20	30	43	Futility at First Three Looks	Futility at End of Study	Efficacy at End of Study	Average Overall Sample Size[1]
Stopping Boundary (No. of Responders)		0	1	3	6				
Assumed True Underlying ORR	0.05	0.60	0.19	0.16	0.05	0.95	1.00	0.00	11
	0.10	0.35	0.13	0.21	0.19	0.69	0.88	0.12	22
	0.15	0.20	0.07	0.13	0.19	0.40	0.59	0.41	32
	0.20	0.11	0.03	0.06	0.10	0.20	0.30	0.70	38
	0.25	0.06	0.01	0.02	0.03	0.09	0.12	0.88	41
	0.30	0.03	0.00	0.01	0.01	0.04	0.04	0.96	42

ORR = Objective Response Rate, N = Sample size; No. = Number
[1]Without considering newly enrolled participants while the interim evaluation is ongoing.

As can be seen from the above table, the probabilities to stop for futility early if true ORR is either 5% or 10% are approximately 100% and 88%, respectively. The probabilities to stop for futility when true ORR is either 25% or 30% are approximately 12% and 4%, respectively. For various criteria to claim efficacy, the exact 95% CI for different corresponding observed ORR are listed in Table 12. For example, if the total sample size is 20 at the second interim evaluation, the lower bound of the 95% CI will be 27.2% if the observed ORR is 50%. When the total sample size is 30 or higher and the observed ORR is 50%, the lower bound of the 95% CI will be ≥31.3%.

Table 12: Exact 95% CI Given Observed ORR

Minimum ORR to Claim Efficacy	Sample Size	Observed No. of Responders	Observed ORR (%)	95% Confidence Interval	
				Lower Bound	Upper Bound
0.25	10	3	30.0	6.7	65.3
	20	5	25.0	8.7	49.1
	30	8	26.7	12.3	45.9
	43	11	25.6	13.5	41.2
0.3	10	3	30.0	6.7	65.3
	20	6	30.0	11.9	54.3
	30	9	30.0	14.7	49.4
	43	13	30.2	17.2	46.1
0.5	10	5	50.0	18.7	81.3
	20	10	50.0	27.2	72.8
	30	15	50.0	31.3	68.7
	43	22	51.2	35.5	66.7

CI = Confidence Interval; ORR = Objective Response Rate

12.3. STATISTICAL ANALYSES

The statistical analysis plan (SAP) will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, spurious data, and intercurrent events that may affect the assessment of the endpoints. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

12.3.1. Efficacy Analyses

All efficacy analyses will be based on treated participants. A brief description of the statistical method for efficacy analyses is summarized in Table 13. Subset analyses for the primary endpoints may be performed for selected baseline characteristics. The details will be described in the SAP.

Table 13: Statistical Method for Efficacy Analyses

Primary Endpoint	**Statistical analysis methods**
Objective response rate, defined as the proportion of participants with CR + PR using RECIST v1.1	The response rate will be calculated, and the exact 95% CI will be provided. The proportion and 95% CI of participants with CR, PR, Stable Disease (SD), and Progressive disease (PD) will also be summarized and listed by visit.
Secondary Endpoint	**Statistical analysis methods**
Estimate of proportion of participants who have not progressed or died at 6 months of follow-up: PFS-6. Progression is defined by RECIST v1.1	The Kaplan-Meier (K-M) method will be used to estimate PFS-6.
Estimate the 2-year overall survival, defined as the proportion of participants who have not died after 2 years of follow-up after their first dose of nirogacestat	The K-M method will be used to estimate the distribution of overall survival
Change from baseline in FOSI	Change from baseline in the FOSI score and the individual responses will be summarized at each cycle, end of treatment, and the follow-up visit.
DoR, defined as the time from first assessment of response (CR + PR using RECIST v1.1) to first disease progression defined by RECIST v1.1 or death, whichever comes first	The K-M method will be used to estimate the distribution of the duration of response including median.
Exploratory Endpoint	**Statistical analysis methods**
Exploratory endpoint statistical analysis method will be described in the SAP.	

CI = Confidence interval; CR = Complete response; FOSI = Functional Assessment of Cancer Therapy – Ovarian Symptom Index; K-M = Kaplan-Meier; ORR = Objective Response Rate; PFS = Progression-Free Survival; PR = Partial Response; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; SAP = Statistical Analysis Plan

12.3.2. Safety Analyses

All safety analyses will be performed on participants who received at least one dose of nirogacestat.

The safety and tolerability of nirogacestat will be evaluated by means of treatment-emergent AEs, physical examinations, and laboratory safety evaluations. Adverse Events will be graded by the Investigator according to the CTCAE v5.0 and coded using the Medical Dictionary for Regulatory Activities.

The focus on AE summaries will be on Treatment-Emergent AEs, those with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. The number and percentage of participants who experienced an AE, SAE,

treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades.

Summaries of clinical laboratory parameters will be summarized by study visit and overall, including absolute results and changes from baseline. Tables for the shift in CTCAE severity grade of laboratory data from baseline to the worst post-baseline value and from baseline to each visit will be presented.

Vital signs data will be summarized by study visit and overall using descriptive statistics. Summaries will be presented for the observed value, the change from baseline value, and the change from baseline to the worst post-baseline value during the treatment period.

The observed ECG values and change from baseline values, and the change from baseline to the worst post-baseline value during the treatment period will be summarized descriptively. The overall ECG assessments will be summarized categorically (normal, abnormal without clinical significance, and abnormal with clinical significance) as a shift table by study visit.

12.3.3. Other Analyses

Pharmacokinetic, pharmacodynamic, and exploratory analyses will be described in the SAP (to be finalized before database lock). The population PK analysis and pharmacodynamic analyses will be presented separately from the main Clinical Study Report (CSR).

12.4. INTERIM ANALYSES

No formal interim analysis is planned. This study will use a Bayesian approach of continuous monitoring for early futility stopping based on ORR, intended to limit the accrual of participants to an ineffective treatment (Section 12.2). The Statistical Analysis Plan will describe the planned continuous monitoring in greater detail.

12.4.1. Data Monitoring Committee

There is no Data Monitoring Committee for this study.

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

A1-1. REGULATORY AND ETHICAL CONSIDERATIONS

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Regulation (EU) no. 563/2014
- Applicable laws and regulations

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

The Investigator will be responsible for the following:

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

A1-2. FINANCIAL DISCLOSURE

Principal Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A1-3. INFORMED CONSENT PROCESS

The Investigator or his/her representative will explain the nature of the study to the participant or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date/time the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form (ICF).

Participants must be re-consented to the most current version of the ICF(s), as per IRB/IEC guidance, during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A1-4. DATA PROTECTION

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Participants must be informed that their medical records may be examined by Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Sponsor maintains robust technical security measures in relation to its systems and by implementing security procedures concerning the handling of sensitive information. The Sponsor maintains data incident response policies governing how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems each a "Data Issue". Sponsor, in consultation with the DPO, will assess the Data Issue as soon as possible and will undertake mitigation measures to contain the Data Issue to prevent further impact, including shutting down affected applications or third-party connections, reconfiguring firewalls, changing computer access codes, and modifying physical access controls. Sponsor will determine if an intruder has exported or deleted any information. Sponsor may use the FRM-0128, Data Incident Reporting Form to document the Data Issue and share relevant documentation with the DPO as it pertains

to Data Issues affecting EEA, Switzerland or UK Data Subjects. Sponsor will provide notice of the Data Issue to impacted data subjects in accordance with Applicable Laws.

A1-5. DATA QUALITY ASSURANCE

All participant data relating to the study will be entered into the electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or onsite monitoring) will be indicated in the monitoring plan to ensure the protocol and GCP is followed.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator according to specifications in the ICH guidelines, local regulations, or as specified in the clinical trial agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A1-6. SOURCE DOCUMENTS

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

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

A1-7. STUDY AND SITE CLOSURE

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

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

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Conditions that may warrant early study site closure but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to participants participating in the study;
- A negative change in the risk/benefit assessment;
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator; or
- The decision on the part of the Sponsor to suspend or discontinue nirogacestat development.

A1-8. PUBLICATION POLICY

Following completion of the trial, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the trial confidential. The Investigator must consult with the Sponsor before any trial data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

APPENDIX 2. PROHIBITED CONCOMITANT MEDICATIONS

A listing of cytochrome P450 (CYP3A4) inhibitors/inducers, P-glycoprotein (P-pg) inhibitors/inducers, protein pump inhibitors (PPIs), and H2 receptor antagonist will be provided in the Study Reference Manual. Contact the Medical Monitor for questions.

APPENDIX 3. RECIST CRITERIA V1.1

For full guidelines, see RECIST Criteria v1.1 (Eisenhauer 2009)

Categorizing lesions at Baseline:

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

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

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

Methods of Measurement

CT or MRI must be used to measure target lesions selected for response assessment. Conventional CT and MRI will be performed with cuts of 10 mm or less in slice thickness contiguously.

Recording Tumor Assessments

All sites of disease must be assessed at Screening. Screening assessment must be done within 28 days of starting study treatment. For an adequate screening assessment, all required scans must be done within 28 days prior to first dose of study treatment and all disease must be documented appropriately.

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

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

Response Criteria: Evaluation of target lesions

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

Evaluation of best overall response

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

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=Complete Response; NE=Not Evaluable; PD=Progressive Disease; PR=Partial Response; SD=Stable Disease.

Participants with a global deterioration of health status requiring discontinuation of study treatment without objective evidence of disease progression at that time will be classified as

having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Confirmation

- **Confirmation of response:**
    - The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
    - To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met.
- **Confirmation of SD:** in the case of SD, follow-up measurements must have met the SD criteria at least once after study entry (signing of Informed Consent Form [ICF]) at a minimum interval of 8 weeks.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

APPENDIX 4. SAFETY ASSESSMENTS

A4-1. CLINICAL LABORATORY TESTS

The tests detailed in Table 14 will be performed by the local laboratory with the exception of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, Inhibin A, Inhibin B, Anti-Müllerian hormone/Müllerian inhibiting substance, and CA-125, which will be sent to a central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 7 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Pregnancy testing (urine as described in the SoA [Schedule of Assessments]; Section 1.3) will be conducted at monthly intervals for WOCBP.

Serum pregnancy tests may be conducted in place of urine pregnancy tests throughout the study if required by local regulations.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Investigators must document their review of each laboratory report.

Table 14: Protocol-Required Laboratory Assessments

Laboratory assessments	Parameters
Hematology	Platelet count
	Hemoglobin
	Hematocrit
	Red blood cell count
	Red blood cell indices: • Mean cell volume • Mean cell hemoglobin
	White blood cell count with differential[1]: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical Chemistry[2]	Blood urea nitrogen
	Potassium
	Total and direct bilirubin
	Creatinine
	Sodium
	Aspartate Aminotransferase (AST) or Serum Glutamic-Oxaloacetic Transaminase (SGOT)
	Alanine Aminotransferase (ALT) or Serum Glutamic-Pyruvic Transaminase (SGPT)
	Gamma-glutamyl transferase
	Total protein
	Albumin
	Chloride
	Bicarbonate
	Glucose (non-fasting)
	Calcium
	Magnesium
	Inorganic phosphorous
	Estimated glomerular filtration rate (eGFR)[3]
	Uric acid
	Alkaline phosphatase

Laboratory assessments	Parameters
Routine Urinalysis	Specific gravity
	potential hydrogen (pH), glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
	Microscopic examination (if blood or protein is abnormal)[4]

Other Tests	Serology[5]
	• HIV antibody
	• HBV
	  ○ HBsAg
	• HCV
	  ○ Hepatitis antibody (HCV PCR if hepatitis C antibody positive)
	Hormone Levels[6]
	• FSH
	• LH
	• Estradiol
	• Progesterone
	Tumor Markers
	• Inhibin A
	• Inhibin B
	• AMH/Müllerian inhibiting substance
	• CA-125

ALT = Alanine Aminotransferase; AMH = Anti-Müllerian Hormone; AST = Aspartate Aminotransferase; CA-125 = Cancer Antigen 125; FSH = Follicle-stimulating hormone; HBV = Hepatitis B virus; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; LH = Luteinizing Hormone; PCR = Polymerase chain reaction; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase

[1]Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

[2]Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 9.1.1 and Appendix A4-3.

[3]Only required at Screening to establish eligibility and/or Baseline and permit full investigation of clinical observations on study. eGFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. See Appendix A4-5.

[4]Microscopy examination is performed only if blood or protein is abnormal.

[5]Serology only required at Screening

[6]Participants reporting Adverse Events (AEs)/Adverse Events of Special Interest (AESIs)/Serious Adverse Events (SAEs) of reproductive system disorders will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).

A4-2. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE

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

Source: (Oken et al. 1982)

A4-3. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

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

Suggested Actions, Follow-up Assessments, and Monitoring

Actions

- **Immediately** discontinue study treatment (nirogacestat)
- Report the event to the Sponsor **within 24 hours**
- Complete the liver event in the electronic Case Report Form (eCRF) and complete the SAE eCRF form if the event also met the criteria for an SAE[2]
- Perform liver chemistry follow-up assessments
- Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**)
- Restart/rechallenge is **not allowed per protocol and not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments

Follow-Up Assessments
• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2×ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF page • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF page • Record alcohol use in the eCRF if AE is related to alcohol use **If ALT ≥ 3×ULN AND bilirubin ≥ 2×ULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total Immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct High performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week (James, 2009). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver • Notify the medical monitor within **24 hours** of learning of the abnormality to discuss participant safety • Participant can continue study treatment • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize or return to baseline • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 9.1.1 If, after 4 weeks of monitoring, ALT < 3×ULN and bilirubin < 2×ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline
Monitoring
If ALT ≥ 3×ULN AND bilirubin ≥ 2×ULN or INR > 1.5: • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT ≥ 3×ULN AND bilirubin < 2×ULN and INR ≤ 1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline ALT ≥ 3×ULN and < 5×ULN **and** bilirubin < 2×ULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks

AE = Adverse Event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CPK = Creatine phosphokinase; eCRF = electronic Case Report Form; HPLC = High Performance Liquid Chromatography; IgG = Immunoglobulin G; INR = International normalized ratio; LDH = Lactate dehydrogenase; SAE = Serious Adverse Event; ULN = Upper Limit of Normal;

[1] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation

testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.

[2] All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (> 35% direct bilirubin) or ALT ≥ 3xULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

[3] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

[4] Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

A4-4. CORRECTED QT INTERVAL (QTC) PROLONGATION RISK

Refer to the Study Reference Manual for a list of substances have been reported to show risk of QTc interval prolongation in published literature or have been demonstrated to have QT effects and risk of effect on cardiac repolarization in clinical studies.

A4-5. CKD-EPI CREATNINE EQUATION

Recommend use of calculator found at:
https://www.kidney.org/professionals/kdoqi/gfr_calculator, which corresponds to the equation below.

Expressed as a single equation:

eGFR =142* min(standardized S_{cr}/K, 1)$^{\alpha}$ *max(standardized S_{cr}/K, 1)$^{-1.200}$ *0.9938^{Age} *1.012 [if female]

Source: CKD-Epi Creatinine Equation, 2021

Abbreviations / Units:

eGFR (estimated glomerular filtration rate) = mL/min/ 1.73 m^2

S_{cr} (serum creatinine) = mg/dL

K = 0.7 (females) or 0.9 (males)

α = -0.241 (females) or -0.302 (males)

min = indicates the minimum of S_{cr}/K or 1

max = indicates the maximum of S_{cr}/K or 1

Clinical Use:

The Recommended method for estimating GFR in adults from the National Kidney Foundation is the 2021 CKD-EPI equations.

Designed for use with laboratory creatinine values that are standardized to IDMS. (See "About GFR" button.)

Estimates GFR from serum creatinine, age and sex

More accurate than the MDRD Study equation, particularly in people with higher levels of GFR.

The CKD-EPI equation is modeled using least squares linear regression to relate log transformed measured GFR to log-transformed filtration markers, age and sex with two slope splines for creatinine.

Some clinical laboratories are still reporting GFR estimates using the MDRD Study equation. The National Kidney Foundation has recommended that clinical laboratories should begin using the 2021 CKD-EPI equation to report estimated GFR using creatinine and cystatin C.

APPENDIX 5. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

A5-1. DEFINITIONS

A5-1.1. ADVERSE EVENT (AE)

An Adverse Event (AE) is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events meeting the AE definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, hormone levels, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/Serious Adverse Event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Any surgeries and/or procedures that were scheduled prior to obtaining the Informed Consent Form (ICF) but occurring afterwards will not be treated as an AE or SAE, unless the condition requiring the surgery or procedure worsened.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

A5-1.2. ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Adverse Events of Special Interest (AESIs) are defined as non-serious or serious AEs that is one of scientific and/or medical concern specific to the Sponsor's product for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

A5-1.3. SERIOUS ADVERSE EVENT (SAE)

If an event is not an AE per definition in Appendix A5-1.1, then it cannot be a Serious Adverse Event (SAE) even if serious conditions are met.

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

1. **Results in death**
2. **Is life-threatening**
    - The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. **Requires inpatient hospitalization or prolongation of existing hospitalization**
    - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any

other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

4. **Results in persistent disability/incapacity**
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. **Is a congenital anomaly/birth defect**
6. **Other situations**
    - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

A5-1.4. SPECIAL SITUATIONS

Special Situations are defined as Abuse, Misuse, Occupational Exposure (inadvertent/accidental), Medication Error study product (with or without participant exposure to the study product e.g., study product name confusion).

- **Abuse:** Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- **Misuse:** Situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the protocol.
- **Occupational Exposure:** An exposure to a medicinal product as a result of one's professional or non-professional occupation.
- **Medical Error:** An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the participant.

A5-1.5. ADVERSE DRUG REACTION (ADR), SERIOUS ADVERSE REACTION (SAR) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

- **Adverse Drug Reaction (ADR):**

  An ADR is any noxious and unintended response to a medical product or procedure, for which a causal relationship with the product or procedure is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

- **Serious Adverse Reaction (SAR):**

  A SAR is an SAE for which a causal relationship with the product or procedure is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

- **Suspected Unexpected Serious Adverse Reaction (SUSAR):**

  A SUSAR is a SAR that is judged as unexpected. An event is considered "unexpected" if it is not listed as expected in the reference safety information (RSI) section of the Investigator Brochure (IB) or summary of product characteristics.

A5-2. RECORDING, EVALUATING AND FOLLOW-UP

A5-2.1. RECORDING AES / AESIS / SAES / SPECIAL SITUATIONS

- All required information pertaining to the AE/AESI/SAE/Special Situation will be recorded in the electronic Case Report Form (eCRF).
- All AESIs, SAEs and Special Situations will require additional information to be reported to Safety utilizing paper forms that must be submitted to Safety. Refer to Appendix A5-3 for reporting details.
- **It is not acceptable for the Investigator to send photocopies of the participant's medical records** to Safety in lieu of completion of the AESI/SAE/Special Situation paper forms.
- There may be instances when copies of medical records for certain cases are requested by Safety. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of the medical records before submission to Safety.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/AESI/SAE/Special Situation.

A5-2.2. EVALUATING AEs / AESIs / SAEs / SPECIAL SITUATIONS

A5-2.2.1. Severity

- The Investigator will make an assessment of severity for each AE/AESI/SAE/Special Situation[1] reported during the study and assign it to one of the following categories:
- Grade refers to the severity of the AE. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
    - **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
    - **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)[2].
    - **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3].
    - **Grade 4** Life-threatening consequences; urgent intervention indicated.
    - **Grade 5** Death related to AE.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (Appendix A5-1.3), **not** when it is rated as severe.

[1]Special Situation reports may not have an applicable CTCAE Grade and may be reported without a CTCAE Grade assigned.

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

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

A5-2.2.2. Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of an AE/AESI/SAE/Special Situation.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) when making an assessment.

- For each AE/AESI/SAE/Special Situation, the Investigator **must** document in the medical notes that they have reviewed the AE/AESI/SAE/Special Situation and has provided an assessment of causality.
- There may be situations in which an AESI/SAE/Special Situation has occurred and the Investigator has minimal information to include in the initial report to SpringWorks. However, **it is very important that the Investigator always make an assessment of causality for every event with the initial SAE reporting to Safety** (refer to Appendix A5-3 for reporting details)
- The Investigator may change their opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A5-2.3. FOLLOW UP

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

A5-3. REPORTING

- The preferred method of submitting AESI/SAE and Special Situations information to Safety is to email the scanned paper forms to PV@springworkstx.com. Facsimile transmission is possible. Please refer to the reporting forms for the fax phone numbers for USA and Europe.
- In rare circumstances in the absence of email or facsimile equipment, notification by telephone is acceptable with a copy of the AESI/SAE or Special Situations form sent by overnight mail or courier service. However, initial notification via telephone does not replace the need for the Investigator to complete and sign the AESI/SAE or Special Situations form within the designated reporting time frames.
- The AESI/SAE and Special Situation forms can be found in the Study Reference Manual.
- Contacts for AESI/SAE/Special Situations reporting can be found in Appendix A8-4.

APPENDIX 6. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

A6-1. WOMEN OF CHILDBEARING POTENTIAL (WOCBP) DEFINITION

Women of Childbearing Potential (WOCBP) are defined as women that are considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). For WOCBP, participant must remain abstinent or use 1 highly effective contraceptive method, as described below during the treatment period and for at least 1 week after the last dose of study treatment.

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

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal with 1 of the following:
    a. Documented hysterectomy; or
    b. Documented bilateral salpingectomy; or
    c. Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry. Bilateral tubal occlusion is not considered to be a permanent form of infertility.

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

A6-2. CONTRACEPTION GUIDANCE

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Contraceptive Methods[b] That Have Lower User Dependency

Note: Failure rate of < 1% per year when used consistently and correctly.

- Implantable progesterone-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

  Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

Highly Effective Methods[b] That Are User Dependent

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - Oral
  - Injectable
- Sexual abstinence

  Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

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

b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) Barrier methods such as condoms (male or female) or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream or vaginal suppository must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

A6-3. COLLECTION OF PREGNANCY INFORMATION

Pregnancy information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date but could be longer if needed to confirm the health status of the neonate. If there are any birth defects identified from the pregnancy, an extended period of time for follow-up may be required. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an Adverse Event (AE) or Series Adverse Event (SAE), any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 11.3.5. While the Investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study

APPENDIX 7. GENETICS

A7-1. USE/ANALYSIS OF DEOXYRIBONUCLEIC ACID (DNA)

Genetic variation may impact a participant's response to study treatment, susceptibility to, severity and progression of disease. Therefore, where local regulations and Institutional Review Board (IRB)/Independent Ethics Committees (IEC) allow, a tissue sample will be collected for DNA analysis from all participants.

DNA samples will be used for research related to this study treatment or this indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

DNA samples will be analyzed for mutations that correlate with response to treatment.

Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained until study closure and for up to 10 years after (or other period as per local requirements).

APPENDIX 8. LIST OF CONTACTS FOR STUDY

A8-1. SPONSOR

SpringWorks Therapeutics
100 Washington Blvd
Stamford, CT 06902
United States
Telephone: 212-421-8012

A8-2. CONTRACT RESEARCH ORGANIZATION

Refer to the Study Reference Manual.

A8-3. REFER TO THE STUDY REFERENCE MANUAL.MEDICAL MONITORING

Refer to the Study Reference Manual.

A8-4. SERIOUS ADVERSE EVENT REPORTING

United BioSource Corporation
920 Harvest Drive, Suite 200
Blue Bell, PA 19442
Fax: 866-750-4514
PV@springworkstx.com

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