STATISTICAL ANALYSIS PLAN

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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
AMH	Anti-Mullerian Hormone
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
BID	Twice daily
BMI	Body Mass Index
C	Cycle
CA 125	Cancer Antigen 125
CI	Confidence Interval
C_{max}	Maximum plasma concentration
C_{trough}	Plasma trough concentration
COVID-19	Coronavirus Disease 2019
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
D	Day
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment
FDA	Food and Drug Administration

FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
FSH	Follicle-stimulating hormone
FUP	Follow-up
GCT	Granulosa cell tumors
GOG	Gynecologic Oncology Group
HBV	Hepatitis B virus
HLGT	High Level Group Term
HR	Heart rate
ICF	Informed Consent Form
INR	International normalized ratio
K-M	Kaplan-Meier
LD	Longest diameter
LH	Luteinizing Hormone
MIS	Mullerian Inhibiting Substance
MRI	Magnetic Resonance Imaging
NE	Not evaluable
NGS	Next Generation Sequencing
NICD	Notch Intracellular Domain
No.	Number
ORR	Objective Response Rate
OS	Overall survival
OS-2	Overall survival probability at 2 years
OvGCTs	Ovarian granulosa cell tumors
PD	Progressive Disease or Pharmacodynamics
PFS	Progression free survival
PFS2	Progression free survival 2
PFS-6	Progression-free survival at 6 months
PK	Pharmacokinetics
PR	Partial Response
QRS	QRS complex

QT	Uncorrected QT interval
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fredericia
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SoA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal

1. SUMMARY OF STUDY PROTOCOL

1.1. Introduction and Study Rationale

This document is the statistical analysis plan (SAP) for NIR-OGT-201, a Phase 2 trial of nirogacestat in Patients with Recurrent Ovarian Granulosa Cell Tumors study to assess the anti-tumor activity of nirogacestat in adult participants with relapsed/refractory ovarian granulosa cell tumors (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 participants eventually develop progressive disease 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. In order 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%.

Treatment of granulosa cell tumors with a gamma secretase (GS) inhibitor such as nirogacestat 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.

This SAP further details the statistical analyses to be conducted during and at the end of the study as determined in the protocol. It is designed to outline the methods to be used in the

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

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

1.2. Study Objectives and Endpoints

The study objectives and corresponding analysis endpoints are listed below.

Primary Objectives:	**Primary Endpoints:**
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 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 (Cmax, Ctrough 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 Mullerian 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.

1.3. Study 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 recurrent 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.

The Schedule of Assessments (SoA) is in protocol Section 1.3, Table 2. 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 (Protocol Section 7.1 and 7.2).

Participants will administer 150 mg (3 × 50 mg tablets) of study treatment BID, continuously in 28-day cycles. Participants will remain on study treatment until death, disease progression (unless the participants meet criteria for continued treatment), 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.

All scans will be performed and read locally by the site's radiologist for Tumor assessment as per RECIST v1.1. Same modality used at Screening must be used at each subsequent imaging visits. Baseline scan is defined as scans performed prior to first dose of study treatment. On treatment scans are performed every 8 weeks (C3D1, C5D1, C7D1) for the first 6 months and then every 12 weeks (C10D1, C13D1, etc.) thereafter. Scans may be performed (-) 7 days prior to the visit.

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.

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) (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.

1.4. Sample Size Determination

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.

Since this is a first-in-human proof of concept study for the indication, no formal hypothesis testing or sample size calculation is contemplated. 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 (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 1 below provides results based on 10,000 simulations of probability of early stopping for futility and the expected overall sample sizes.

Table 1 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 based on the Clopper-Pearson method are listed in Table 2. 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 2 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

1.5. Data Monitoring Committee

There is no Data Monitoring Committee for this study.

2. ANALYSIS SETS

2.1. Analysis Set Definitions

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

- Screened Analysis Set: The Screened Analysis Set will consist of all participants who signed the informed consent.
- Full Analysis Set: The Full Analysis Set will consist of all participants who received at least 1 dose of nirogacestat treatment.
- PK Analysis Set: The PK Analysis Set will consist of all treated participants with at least 1 non-missing value in serum concentration of nirogacestat.
- Safety Analysis Set: The Safety Analysis Set will consist of all participants who received at least 1 dose of nirogacestat treatment.

The Full Analysis Set is the same as the Safety Analysis Set. All efficacy analyses will be based on the Full Analysis Set. All safety analyses will be based on the Safety Analysis Set.

2.2. Protocol Deviations

Protocol deviations are reviewed in accordance with the Protocol Deviation Management Plan. All Major and Minor protocol deviations will be reviewed by SpringWorks prior to database lock. The protocol deviation categories are defined in the Protocol Deviation Management Plan, including those related to the inclusion/exclusion criteria, informed consent, withdrawal criteria, study treatment, etc. Major protocol deviations and the COVID-19 related major protocol deviations will be summarized. A data listing of all PDs including a description of the deviation will be generated, and the COVID-19 related protocol deviations will be flagged.

2.3. Impacts from COVID-19

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

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

3. ENDPOINTS

3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is objective response rate, defined as the proportion of participants with CR + PR using RECIST v1.1. See Section 8.1 for the details of RECIST Criteria v1.1.

Study participants who have no post-baseline tumor assessment and those whose best overall response is not evaluable or less than CR or PR will be analyzed as a non-responder.

3.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- PFS-6, defined as the survival probability of not having progressed or died at 6 months follow-up. Progression is defined by RECIST v1.1.
- Two-year overall survival at 2 years (OS-2), defined as the survival probability of being still alive at 2 years of follow-up after their first dose of nirogacestat.
- Change from baseline in FOSI.
- 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.

3.3. Exploratory Efficacy Endpoints

Exploratory endpoints include:

- Progression free survival (PFS), defined as time from first dose of nirogacestat to first disease progression on nirogacestat or death from any cause, whichever comes first.
- Progression free survival on continued 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.
- 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 survival (OS), defined as time from first dose of nirogacestat to death from any cause.
- Time to response, defined as time in months from first dose until date of the first documented response (CR or PR).
- Evaluate Next Generation Sequencing (NGS) status in baseline tumor tissue.
- Change from baseline in:
  - Inhibin A&B, Follicle-stimulating, hormone (FSH), estradiol, CA-125, and Mullerian Inhibiting Substance (MIS) / AMH
  - Circulating tumor DNA (ctDNA) (if data are available)
- Baseline NICD expression in tumor tissue (if data are available).

3.4. Safety Endpoints

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.

3.5. Pharmacokinetic Endpoints

Pharmacokinetic endpoints include C_{trough} and 1-hour post-dose serum concentrations of nirogacestat.

3.6. Other Endpoints

Not applicable.

4. STATISTICAL METHODOLOGY

4.1. General Information

All data listings that contain an evaluation date will have a relative study day associated with treatment start (Rel Day). Pre-treatment and on-treatment study days represented as Relative Day are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

Tabulations will be produced for appropriate disposition, demographic, baseline characteristics, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of participants, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using 25th, 50th (median) and 75th percentiles and time point survival probabilities (at 6 months, 1 year, 18 months, 2 years, etc.) with associated 2-sided 95% confidence intervals (CIs) using Kaplan-Meier methodology and the log-log transformation, as well as number and percentage of events and censored observations.

Graphical displays will be provided where useful to aid in the interpretation of results. A swimmer plot may be used to present the exposure to study treatment, overall response and follow up for all participants in the Full Analysis Set. Each participant will be presented on a horizontal bar (y-axis) over time (x-axis) starting at treatment start date. For each participant's bar, the plot will include best overall response (CR, PR, SD, PD, or NE), end of response or continued response (at censored timepoint).

The following conversion conventions will be applied:

- CIs will be presented to 1 more decimal place than the raw data
- Weeks will be calculated as number of days divided by 7
- Months will be calculated as number of days divided by 30.4375
- Years will be calculated as number of days divided by 365.25
- Cycles as used in adverse event summaries are defined as every 28 days
- Day 1 will be considered as the first day of treatment

All tables, figures, and listings will include footers at the bottom of the page reflecting the path of the programs used to generate the tables, figures, and listings, and date and time of the generation of the output.

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4 or higher. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version March 2022 or later.

4.2. Baseline Definitions

For all analyses, baseline will be defined as the last non-missing value prior to the first administration of study treatment.

4.3. Methods of Pooling Data

Data will be pooled across study sites.

4.4. Adjustments for Covariates

In this single arm study, covariate adjustment will not be used unless specified otherwise.

4.5. Multiple Comparisons/Multiplicity

Since this is a first-in-human proof of concept study for the indication, no formal hypothesis testing is contemplated. Hence there is no multiplicity adjustment for the primary or secondary efficacy endpoints.

4.6. Subgroups

Subgroup analyses for the primary endpoint ORR are not predefined due to the following reasons:

- This is a single arm study with a small sample size.
- The anticipated response rate is low-to-medium.

However, post-hoc analysis for subgroup analyses will be performed if deemed necessary.

4.7. Withdrawals, Dropouts, Loss to Follow-up

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

4.8. Missing Data Conventions for Efficacy Endpoints

There will be no imputation or substitutions made to accommodate missing efficacy data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

4.9. Missing Data Conventions for Safety Endpoints

4.9.1. Handling of Missing/Partial Dates for AEs

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

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

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

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

4.9.2. Handling of Concomitant Therapies/Medications with Missing/Partial Dates

Concomitant medications are defined in Section 5.6.8. Concomitant therapies/medications with start dates that are completely or partially missing will be handled as follows for the propose of determining concomitance.

1. If the start date has the month and year but the day is missing, the therapy will be considered concomitant if the month and year are:
   a. On or after the month and year of the date of the first dose of study treatment
   b. On or before the month and year of the date of the last dose of study treatment plus 30 days
2. If the start date has the year, but the day and month are missing, the therapy will be considered concomitant if the year is:
   a. On or after the year of the date of the first dose of study treatment
   b. On or before the year of the date of the last dose of study treatment plus 30 days.
3. If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is prior to the date of informed consent, then this therapy will not be considered concomitant.
4. If the start date of concomitant therapies is completely or partially missing and the stop date of concomitant therapies is on or after the date of the first dose of study treatment, then the therapy will be considered concomitant.
5. If the start date and stop date of concomitant therapies are completely missing, then the therapy will be considered concomitant if the therapy was reported as a concomitant therapy.

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

To calculate time from diagnosis or most recent prior therapy to informed consent, partial/missing dates for diagnosis and last prior therapy completion will be imputed as follows:

- If both day and month are missing and the year is prior to the year of screening, the imputed day and month will be July 1.

- If both day and month are missing and the year is the same as the year of screening, the imputed date will be the middle point between January 1 of the year and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- If day is missing and the month and year are prior to the month and year of screening, the imputed date will be 15th day of the month.
- If day is missing and the month and year are the same as the month and year of screening, the imputed date will be the middle point between the first date of the month and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- No imputation will be performed if the year is missing.

4.10. Visit Windows

No visit windowing was performed. All visits will be tabulated per the evaluation visit as recorded on the eCRF. Repeat, retest, and unscheduled assessments will not be considered for the calculation of summary statistics and figures, unless assessment qualifies as baseline, or otherwise indicated. These types of assessments will be included in the listings.

5. STATISTICAL ANALYSES

5.1. Disposition

The total number of participants who were screened (who have signed the informed consent), reasons for screen failure and the number in each study population will be summarized based on the Screened Analysis Set.

The end of treatment status (ongoing/discontinued) together with the primary reason for discontinuing the treatment will be summarized as follows:

- Death
- Disease Progression
- Removal From Study (Investigator/Sponsor Decision)
    - Adverse Event
    - Excluded Concomitant Medication or Procedure
    - Compliance (Study Treatment/Study Assessments)
    - New Information/Findings
    - Study/Site is Cancelled
    - Relocation
    - Lost to Follow-Up
    - Other
- Withdrawal of Consent
- Study Completion
- Other

In addition, the end of study status will be summarized including if a participant is participating in the long-term follow-up.

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

5.2. Demographics, Baseline Characteristics, and Medical History

Demographics and baseline characteristics will be summarized for the Full Analysis Set. In addition, medical history (including any history of infertility), disease characteristics, prior systemic treatment, radiation and surgery will also be summarized for the Full Analysis Set. Demographic and baseline data, disease characteristics, and prior systemic treatment for each participant will be provided in data listings. In addition, data listings containing the details for prior surgery coded with MedDRA (version 27.0) and prior radiation will be provided.

5.2.1. Demographics

Demographics will include univariate statistics for age at time of informed consent (years), baseline weight, baseline height, baseline body mass index (BMI) (kg/m^2), baseline FOSI, and categorical summaries for age groups, women of childbearing potential (yes / no), baseline ECOG, race, and ethnicity.

5.2.2. OvGCT History and baseline Characteristics

Baseline disease characteristics to be summarized including time (in months) since date of original OvGCT diagnosis to first study treatment, age at the original disease diagnosis, refractory disease (yes/no), time from refractory (months), relapse (yes/no), time from the original relapsed OvGCT diagnosis and the most recent relapse to first study treatment (months), history of prior surgery for OvGCT (yes/no), time (months) since the most recent surgery to first study treatment, prior radiation (yes/no), time (months) since the most recent radiotherapy to first study treatment, prior systemic treatment (yes/no), time (months) since the most recent prior treatment (surgery, radiotherapy and systemic treatment) to first study treatment, number of target lesions, number of non-target lesions, and baseline tumor size, defined as the sum of the target lesion diameters per RECIST v1.1.

5.2.3. Medical History

The following medical history will be summarized:

- time in months since last menstrual cycle to first study treatment,

- number and percentage of participants with any history of amenorrhea, menstrual irregularities, or infertility, and
- any clinically significant past or ongoing medical conditions, by MedDRA (version 27.0) System Organ Class (SOC) and Preferred Term (PT).

5.2.4. Prior Systemic Therapies for OvGCT

Prior systemic therapies for OvGCT will be coded with WHO Drug March 2022 version or higher and will be summarized by anatomic therapeutic class (ATC) and PT.

Details about each line of treatment, including agents start and stop date, reason for discontinuation, best overall response will be listed. The number of lines of systemic treatment, prior use of Bevacizumab (yes/no), time (months) since most recent Bevacizumab use and time (months) since most recent systemic treatment line to first study treatment will be summarized along with other disease characteristics.

5.3. Primary Efficacy Endpoint

All efficacy endpoints will be analyzed using the Full Analysis Set. The primary efficacy endpoint is objective response rate, defined as the proportion of participants with CR + PR. Tumor response and progression of cancer under study in real time will be evaluated locally at each study site according to RECIST v1.1.

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. In order for a valid value of Stable Disease (SD) to be assigned, there must be evidence of stable disease for at least 7 weeks (the 8-week scan interval inclusive of a 1-week window per the SoA) from start of treatment. If the minimum time for SD has not been met on the first assessment, the assignment of BOR will depend on subsequent response assessments. Participants who do not have follow up data after a first assessment of SD prior to the minimum time requirement will be considered as not evaluable (NE).

The best overall response is determined by the following hierarchy: CR > PR > SD > PD > NE. Participants with a best overall response as confirmed CR or PR during the study will be

responders. Participants who had no post-baseline tumor assessment and those whose best overall response is no evaluable or less than CR or PR will be analyzed as non-responders.

5.3.1. Analysis of Objective Response Rate

The objective response rate and its 95% CI based on the Clopper-Pearson method will be provided. The proportion and 95% CI of participants with CR, PR, Stable Disease (SD), Progressive disease (PD) and Not Evaluable (NE) as defined by RECIST v1.1 will also be summarized and listed by visit.

Tumor size, defined as the sum of the target lesion diameters per RECIST v1.1, will be summarized as percent change from baseline by visit. In addition, the percent change from baseline in the sum of target lesion diameters as identified by RECIST v1.1 by the best overall response will be displayed graphically using a waterfall plot.

5.3.2. Sensitivity Analyses of Objective Response Rate

There is no sensitivity analysis of objective response rate. Post hoc analyses may be performed if deemed necessary.

5.3.3. Subgroup Analysis for Objective Response Rate

See Section 4.6 for subgroup analysis.

5.4. Secondary Efficacy Endpoints

Analysis of secondary endpoints will be conducted using the Full Analysis Set.

5.4.1. PFS-6

PFS-6 will be estimated using Kaplan-Meier method and 2-sided 95% CI based on log-log transformation. Participants who do not progress or die will be censored according to the censoring rules for the PFS as outlined in Table 3.

5.4.2. OS-2

The Kaplan-Meier method will be used to estimate the OS-2. Death due to any reasons will be an event. Participants who did not die at 2 years will be censored.

5.4.3. Change from Baseline in FOSI-8

Functional Assessment of Cancer Therapy (FACT) Ovarian Symptom Index-8 item version (FOSI-8) was used in this study for description of each item in FOSI-8 version 4, see Section 8.2.

Participants are asked to circle or make one number per statement to indicate their response as it applies to the past 7 days. In each statement, the numbers and meaning are as follows: 0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, 4 = Very much. Except for statement 7 (I am content with the quality of my life right now), a lower number in the answer indicates a better condition. The response to the statements except for the statement 7 will be reversed and the sum of non-missing responses will be calculated.

The total FOSI-8 score will be summarized as sum of (8 question items) x 8 divided by the number of items answered. The FOSI-8 total score will range from 0 to 32 and a higher score is good. Therefore, a score of "0" is a severely symptomatic participant and the highest possible score is an asymptomatic participant. The FOSI-8 total score will be set to missing if 5 or more of the 8 item responses are missing.

Summary statistics of change from baseline in the FOSI-8 total score and the individual item responses will be summarized for each visit. In addition, the proportion of participants who achieved ≥ 2 improvement in FOSI-8 total score from baseline (Beaumont et al. 2007) will be summarized by each visit. Participants who could not possibly improve by at least 2 points due to a high score at baseline will be excluded from this analysis. A box and whisker plot displaying the total score over time by nominal visit and a figure for median change from baseline overtime will also be provided.

To evaluate association between changes of tumor size over time and the FOSI-8 total score, a figure with the percent change from baseline in tumor size on one y-axis and the change from baseline in FOSI-8 total score on a secondary y-axis over time (x-axis) will be generated.

5.4.4. Duration of Response (DoR)

DoR will be summarized with standard summary statistics and will also be analyzed using the Kaplan-Meier method for confirmed responders only. Quartiles (i.e., the 25th, 50th, and 75th percentile estimates) and the 2-sided 95% confidence intervals will be presented. If progression

or death was not observed, the participant will be censored according to the censoring rule for PFS (see Table 3). If there are censored participants in DoR, time to censoring will be used to summarize the range. The Kaplan-Meier plot will be provided.

By-participant listing will be provided for responders. The listing will include number of completed cycles before first response, date of first response, date of first disease progression or death if any, censored or event will be marked.

5.5. Exploratory Efficacy Endpoints

5.5.1. Time to Event Endpoints

Exploratory time to event endpoints include PFS, PFS on continued treatment, PFS2 and OS.

For each endpoint, quartiles (i.e., the 25th, 50th, and 75th percentile estimates) and the 2-sided 95% confidence intervals will be calculated from the Kaplan-Meier method. Survival probability and associated 95% CIs will be estimated at 6 months, 1 year, 18 months and 2 years as well. The number of events, number of participants censored, number of participants for each reason of censoring will be provided. The Kaplan-Meier plot of the survival distribution function will be presented with the number of participants at risk over time.

PFS

For PFS, participants who have no documented disease progression and death will be censored according to the rules in Table 3. For PFS-6 and DoR, similar censoring rules should be used if applicable.

Table 3 PFS and DoR censoring rules

Situation	Date of Censoring or Event	Outcome
No adequate tumor assessment at baseline or post-baseline and the participant has not died	Date of first dose of study treatment	Censored
No documented progression or death	Date of last adequate disease status assessment	Censored

Situation	Date of Censoring or Event	Outcome
Progression based on RECIST v1.1 with ≤1 missing consecutive scheduled tumor assessment before progression	Date of the earliest assessment that results in a finding of progression	Event
Death without documented progression with ≤1 missing consecutive scheduled tumor assessment before death	Date of death	Event
New anticancer therapy or procedure started prior to documented disease progression	Date of last adequate disease status assessment before the new therapy	Censored
Progression/Death after two or more missing scheduled tumor assessments	Date of last adequate disease status assessment before the missed assessments	Censored

Progression-free survival on continued nirogacestat treatment and PFS2

For the PFS analysis on continued nirogacestat treatment, only participants who continued the study treatment after the initial evidence of disease progression will be included. Participants who are alive and have not had a second progression will be censored at the last adequate disease status assessment date.

For PFS2, the second disease progression after participants discontinued the study treatment following the initial evidence of disease progression, and started the subsequent line of anticancer treatment, or death, whichever occurs first, will be considered as events for the PFS2 analysis. Participants who are alive and have not had a second progression on subsequent line of anticancer treatment will be censored at the last adequate disease status assessment date.

OS

For OS, in participants who have died, death will be considered an event and the death date will be used to calculate the time. For participants who are alive at the time of analysis, who are lost to follow-up or who withdraw consent for follow-up, the OS endpoint will be censored on the last date that participants were known to be alive or lost to follow-up.

5.5.2. Next Generation Sequencing status

The NGS status will be assessed at baseline to detect FOXL2 C134W mutation as well as other genomic alterations and correlate these with response. A 2×2 table will be generated for FOXL2 C134W mutation (yes/no) vs. Objective Response (yes/no) to evaluate the correlation between mutation and ORR with the Spearman rank correlation and its 95% CI provided. Within each status, the percentage of participants with objective response (CR + PR) and its 2-sided exact 95% CI based on the Clopper-Pearson method will be provided. The response ratio of participants with alteration vs. those without alteration and its 95% CI will also be provided using the Farrington-Manning method.

NGS status data will be listed. Correlation between ORR and other genomic alterations will be analyzed post hoc if deemed necessary.

5.5.3. Inhibin A&B, Follicle-stimulating Hormone, Estradiol, CA-125, and AMH/Mullerian Inhibiting Substance (MIS)

Tumor and hormonal markers Inhibin A, Inhibin B, AMH/MIS, follicle-stimulating hormone, estradiol, and CA-125 will be assessed per the SoA (see Table 2 in the protocol). Summary statistics and change from baseline at each visit will be provided. Box and whisker plots displaying the values over time by nominal visit will also be provided.

To evaluate association between changes in tumor size over time with FSH and estradiol level, a figure with the percent change from baseline in tumor size on one y-axis and the change from baseline in FSH and estradiol level on a secondary y-axis over time (x-axis) will be generated.

5.5.4. Time to Response

Time to first objective response will be calculated as time in months from first dose until date of the first documented response (CR or PR). Only participants with confirmed response will be included and the time in months to first response will be summarized with standard summary statistics.

5.6. Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set.

5.6.1. Study Dug Exposure and Compliance

Extent of exposure will be summarized as follows:

- Duration of exposure in months (last dose of study treatment date – first dose date + 1 /30.4375) summarized as a continuous variable
- If a data cut-off date is used and some participants are receiving treatment at the time of analysis, the last dose date at the time of the data cut-off for analysis will be the data cut-off date
- Number and percentage of participants who received treatment with a duration of at least 1 cycle (28 days), 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 to 12 cycles, 13 to 25 cycles and 26 cycles or longer
- Actual dose intensity (mg/day) – calculated as the cumulative dose received / duration of exposure in days
- Relative dose intensity (%) defined as 100 × (total cumulative dose received)/ (planned cumulative dose, where planned cumulative dose is 300 mg/day multiplied by duration of exposure in days) and summarized as a continuous variable
- Number and percentage of participants with a dose modification (dose reduction and/or dose interruption as reported on eCRF) as well as reasons for dose modification
- Number and percentage of participants with a dose reduction (as reported on eCRF)
- Time (in days) to the first dose reduction and first dose interruption will be summarized as continuous variables
- Number and percentage of participants with a dose interruption including the number of days interrupted
- Number and percentage of participants with study treatment discontinued
- Special Situations in exposure are defined as Abuse, Misuse, Occupational Exposure (inadvertent/accidental), or Medication Error of study treatment. The number and percentage of participants with each and overall special situations resulting in an adverse event will also be summarized.

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

5.6.2. Adverse Events

All AEs will be coded using the MedDRA coding dictionary version 27.0 and displayed in tables and data listings using system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent adverse events (TEAEs), defined as 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 imputation of partial/missing dates is described in Section 4.9.1.

Treatment-related TEAEs are defined as a TEAE that was considered by the Investigator to be related to the study treatment. If "Relationship to Study Treatment" is missing, it will be imputed as related in summary tables.

AE 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).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- 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 (Protocol Appendix A5-1.3), not when it is rated as severe.

A summary of TEAEs will include the number and percentage of participants who experience at least one of the following. The total number of events will also be reported.

- TEAEs

- TEAEs related to study treatment
- Serious TEAEs
- Serious TEAEs related to study treatment
- Serious TEAEs by maximum severity (Grade)
- TEAEs with CTCAE grade ≥ 3
- TEAEs with CTCAE grade ≥ 3 related to study treatment
- TEAEs by maximum severity (Grade)
- TEAEs leading to early discontinuation from study treatment
- TEAEs leading to early discontinuation from study treatment related to study treatment
- TEAEs leading to dose reduction
- TEAEs leading to dose reduction related to study treatment
- TEAEs leading to dose interruption
- TEAEs leading to dose interruption related to study treatment
- TEAEs leading to dose reduction or interruption
- TEAEs leading to dose reduction or interruption related to study treatment
- TEAEs leading to death
- TEAEs leading to death related to study treatment
- TEAEs by cycle of onset

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

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

A TEAE summary by PT only and sorted by descending frequency will also be produced.

All AEs will be listed in participant data listings. By-participant listings will also be provided for the following: TEAEs leading to death, serious adverse events, TEAEs leading to study treatment withdrawn, and TEAE leading to discontinuation from study.

5.6.3. Safety Topics of Special Interest

Safety topics of special interest have been identified based on review of safety data from prior studies with nirogacestat and include additional AEs beyond those specified in Protocol Section 11.3.1 as adverse events of special interest (AESIs). These safety topics of interest, including AESIs determined by the investigators for this study, will be summarized on separate tables. These safety topics, including AESIs, are defined for analysis purposes in different ways, including by using standardized MedDRA queries (SMQ) or customized MedDRA queries, and whether an investigator determined that an event was an AESI.

Unless specified otherwise, the incidence of AESIs based on the investigator's determination will be summarized by SOC and PT in tables and listed separately in participant data listings, and those by using defined lists of specific MedDRA PTs without regard to the investigator's designation of the reported event as an AESI will be summarized similarly.

For the safety topics of special interest (including AESIs) defined using standardized MedDRA queries (SMQ) or customized MedDRA queries, the specific MedDRA PTs for inclusion are all listed in Appendix 8.4 under the following groups. Safety topics for which narrow and broad terms are identified, only narrow terms are used for summary tables. The safety topics will be summarized by SOC and PT based on the Safety Analysis Set.

- Hypersensitivity
- Skin Disorder and Rash
- Hepatotoxicity
- Electrolyte Disorder
- Non-melanoma Skin Cancer
- Musculoskeletal Disorders
- Bone Fractures
- Mucositis/Stomatitis

- Hematologic Disorders
- Opportunistic Infections
- Central Nervous System Vascular Disorders
- Embolic and Thrombotic Events
- Cardiac Rhythm Disturbances
- Upper Respiratory Tract Infections
- Diarrhea

In addition to the summaries by SOC and PT as described above, separate summaries for concomitant medication use will be presented for the following safety topics:

- Hypophosphataemia (A subset of Electrolyte Disorder terms)
- Upper Respiratory Tract Infection
- Diarrhea
- Skin and Subcutaneous Rash (Broad and Narrow; a subset of Skin Disorder and Rash terms)
- Skin and Subcutaneous Rash (Narrow; a subset of Skin Disorder and Rash terms)

The number and percentage of participants with concomitant medication used for each safety topic of special interest will be presented by ATC Classification, Preferred Term and Grade (1-2 vs. ≥3). The following will be also summarized:

- Number and percentage of participants with the safety topic of special interest
- Time to Onset of First Instance of the safety topic of special interest (days)
- Duration of the safety topic of special interest (days) for each event
- Time from onset of first instance of the safety topic of special interest to resolution of last event
- Number of participants with the safety topic of special interest by outcome, grade (1-2 vs. ≥3), and dose modification (if any)
- Number and percentage of participants with concomitant medication use for the safety topic of special interest
- Duration of concomitant medication use for the safety topic of special interest (days)

If an adverse event is ongoing, the end date will be imputed as the data cut-off date for the duration calculation. The duration of concomitant medication use is defined as the number days a participant took medications for the safety topic of special interest. If multiple concomitant medications are taken on a given day, that day will be counted once in the sum. If a medication is ongoing, the end date will be imputed as the last visit date + 28 days (if not before the medication start date), or the study treatment end date if unavailable.

5.6.4. Protocol-Required Laboratory Assessments

Protocol-required laboratory parameters are listed in Table 13-1 in the protocol. The tests in this table will be performed by the local laboratory except for follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, Inhibin A, Inhibin B, Anti-Mullerian hormone/Mullerian inhibiting substance (AMH/MIS), and CA-125, which will be sent to a central laboratory.

Clinical laboratory values will be expressed in international system of units (SI) units. Summaries of clinical laboratory parameters will be summarized by study visit and overall. Tables for the shift of laboratory data from baseline to the worst post-baseline value will be presented for each lab parameter. The shift from baseline to each visit will also be presented for hematology and chemistry parameters.

The actual value and change from baseline will be summarized for each visit for clinical hematology and chemistry. For analysis of tumor markers and hormones, see Section 5.5.3.

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

Additional shift tables will be produced for ALT, AST, alkaline phosphatase, bilirubin, phosphorus, and creatine showing shifts of below normal range, within normal range, >1 to 2 × upper limit of normal range, >2 to 3 × upper limit of normal range, >3 to 5 × upper limit of normal range, to > 5 × upper limit of normal range from baseline to the worst (highest) post baseline value.

Box and whisker plots displaying the values over time by nominal visit will be produced for the hematology and clinical chemistry lab tests.

All laboratory results will be listed and laboratory tests with an abnormal result will be flagged. A subset listing will be presented for all grade 3 or higher laboratory values.

A summary table and a listing of participants meeting liver chemistry stopping criteria will be provided by the cycle of onset and overall. These are participants with the following conditions:

- ALT ≥5×ULN
- ALT ≥ 3×ULN persists for ≥ 4 weeks
- ALT ≥ 3×ULN and bilirubin ≥ 2×ULN (> 35% direct bilirubin)
- ALT ≥3×ULN and International normalized ratio (INR) > 1.5, if INR measured
- ALT ≥ 3×ULN and cannot be monitored weekly for 4 weeks. Missing lab values within window will be considered not monitored.
- ALT ≥ 3×ULN associated with symptoms (new or worsening) believed to be related to liver

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

5.6.5. Physical Exam and Eastern Cooperative Oncology Group Performance Status

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

Shift tables will be used to summarize the count and frequency for each shift of baseline ECOG performance status grade to the worst and the best post-baseline ECOG grade. The ECOG performance status grades are outlined in Table 4.

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

Table 4 Eastern Cooperative Oncology Group Performance Status Grades

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

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

5.6.6. Electrocardiogram

The actual value and change from baseline at each time point will be summarized for 12-lead ECG parameters. The 12-Lead ECG parameters include heart rate, PR, RR, QRS, QT and QTcF intervals.

Categorical groups of QTcF will be summarized as follows:

- Maximum post-baseline QTcF
  - ≤ 450 msec
  - > 450 and ≤ 480 msec
  - > 480 and ≤ 500 msec
  - > 500 msec

- Maximum change from baseline for QTcF
  - ≤ 30 msec
  - > 30 and ≤ 60 msec
  - > 60 msec
- Baseline QTcF < 450 msec and post-baseline QTcF > 500 msec
- Baseline QTcF between 450 and 480 msec and post-baseline QTcF ≥ 530 msec

ECG parameters will be summarized by visit and the worst post-baseline change from baseline. All ECG data will be included in a by-participant data listing. Listings will be provided for participants with abnormal or outlying values for QTcF and changes in QTcF.

5.6.7. Vital Signs

The actual value and change from baseline for all parameters (blood pressure, respiratory rate, heart rate, and body temperature) will be summarized at each scheduled visit.

Potentially clinically significant post-baseline vital signs will also be summarized following the criteria as below:

- Systolic Blood Pressure (mmHg)
  - Value ≥ 150
  - Increase of 20 from baseline
  - Value ≥ 150 and increase of 20 from baseline
  - Value < 90
  - Decrease of 20 from baseline
  - Value < 90 and decrease of 20 from baseline
- Diastolic Blood Pressure (mmHg)
  - Value ≥ 95
  - Increase of 10 from baseline
  - Value ≥ 95 and increase of 10 from baseline
  - Value < 60
  - Decrease of 10 from baseline
  - Value < 60 and decrease of 10 from baseline

- Heart Rate (beats/min)
  - Value ≥ 110
  - Increase of 20 from baseline
  - Value ≥ 110 and increase of 20 from baseline
  - Value ≤ 50
  - Decrease of 20 from baseline
  - Value ≤ 50 and decrease of 20 from baseline
- Temperature (°C)
  - Value ≥ 38
  - Value < 35

Vital sign measurements will be summarized by visit and the worst post-baseline change from baseline. The data listing will be presented for each participant. A summary table and listing will also be provided for participants with potentially clinically significant vital signs.

5.6.8. Concomitant Medications

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 will be recorded along with:

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

Concomitant medications will be coded using the WHO Drug Dictionary March 2022 version or higher. Medications or vaccines that ended before receiving the first study treatment will be considered as the prior medication. Medications or vaccines that continued or started on or after receiving the first dose through 30 days after the last dose of study treatment will be summarized as the concomitant medication. Medication, vaccine or procedure started more than 30 days after the last dose will be considered as subsequent.

The handling of partial/missing start dates for concomitant therapies/medications are described in Section 4.9.2. Concomitant medications will be tabulated by anatomic therapeutic class (ATC) and PT. In these tabulations, each participant will contribute only once to each ATC and PT regardless of number of uses.

The concomitant procedures will be coded using the MedDRA coding dictionary version 27.0 and displayed in tables and data listings using system organ class (SOC) and preferred term (PT).

All medications, vaccines and procedures will be included in data listings. An identifier will be used to show whether a medication, vaccine or procedure was prior, concomitant or subsequent.

5.7. Pharmacokinetic and Pharmacodynamic Analyses

Exploratory analyses maybe conducted based on the data collected, with purposes of providing information for potential pharmacokinetic/pharmacodynamic (PK/PD) analysis if deemed necessary. The specifics of these analyses will be described in a separate PK/PD Analysis Plan and reported separately from the main Clinical Study Report (CSR). For purposes of the CSR for which this SAP provides the basis, serum pharmacokinetic collection dates, times, and concentrations will be displayed in a data listing. Additionally, summaries of the concentrations will be provided.

5.8. Interim Analysis

No formal interim analysis is planned. This study planned to use a Bayesian approach of continuous monitoring for early futility stopping based on ORR Potential timepoints for interim evaluation might occur when 10, 20, and 30 participants had completed 6 months of follow-up or dropped out. At each interim look, an exact 2-sided 95% CI based on the Clopper-Pearson method would also be provided. See Section 1.4 for a brief description of both methods.

This section provides detailed calculation of the Bayesian approach, however, due to the rapid enrollment, the previously planned informal data assessment using this Bayesian approach for early futility stopping based on ORR was no longer feasible as instead of 10 participants, 53 were already enrolled before the one year predicted cutoff time point.

The Bayesian approach to be used for futility analysis assumes a beta-binomial distribution with an uninformative prior of beta distribution. If a random variable *Z* follows a beta distribution with parameters *(α, β)*, the probability density function will be

$$(1) \qquad f(z) = \frac{z^{\alpha-1}(1-z)^{\beta-1}}{B(\alpha,\beta)},$$

where potential values of *z* are in (0,1),

$$(2) \qquad B(\alpha,\beta) = \Gamma(\alpha)\Gamma(\beta)/\Gamma(\alpha,\beta),$$

and Γ is the Gamma function, i.e., $\Gamma(\alpha) = \int_0^\infty t^{\alpha-1}e^{-t}dt$. The mean of *Z* is $\alpha/(\alpha+\beta)$.

At the first interim look, the prior of ORR is assumed to follow a beta distribution with parameter (0.1, 0.9). Hence the corresponding mean is 0.1. 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* (Lee and Liu 2008; Chen et al. 2019). For example, if 2 out of 10 participants are responders at the first interim look, the updated prior of ORR will follow a beta distribution with parameters (2.1, 8.9), which has a mean of 2.1/11=19.1%. Hence, the initially assumed beta prior with parameters (0.1, 0.9) does not have substantial impact on the updated prior and is considered non-informative prior.

For the remaining *(43-n)* future participants, the number of responses, *Y*, follows a beta-binomial distribution with parameters *(43-n, a+x, b+n-x)* (Lee and Liu 2008). Since *a, b, n, x* are known at this point, the probability Pr(*Y=i*) can be calculated using the probability mass function of a beta-binomial distribution. See equation (3) below.

If Z follows a beta-binomial distribution with parameters *(n, a, b)*, the probability of *Z = z* is:

$$(3) \qquad f(z|n,a,b) = \binom{n}{z}\frac{B(z+a,n-z+b)}{B(a,b)}$$

If *i* out of *(43-n)* future participants are responders, the updated prior for ORR will follow a beta distribution with parameters *(0.1+x+i, 0.9-x-i)*. If under the frequentist framework, the null hypothesis is ORR =15%. the posterior probability of ORR >15% can be calculated. Using SAS® CDF function, this probability is:

(4) $\text{pr}(ORR > 0.15|x, Y = i) = 1 - CDF(\text{"Beta"}, 0.15, (0.1 + x + i), (0.9+43\text{-x-i}))$.

Define the predictive probability as the chance of observing any $Y = i$ responders in future participants such that the posterior probability of ORR >0.15 is greater than 85%. If the predictive probability is too low, e.g., ≤10%, the study may be terminated for futility.

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 as follows. After observing a total of *x* out of *n* responders up to an interim look, the possible number of responders, *Y,* in the future will be *0, 1, 2, …, (43-n)*. For each possible $Y = i$, calculate the posterior probability of *Pr_i(ORR >0.15|x, Y=i),* where *i=0, 1, 2, …, (43-n),* using equation (4). If this posterior probability is >0.85, $Y=i$ responders is considered promising. The probability of $Y = i$ can be calculated using equation (3). The predictive probability for ORR >15% with threshold 85% is:

(5) $$Predictive\ probability = \sum_{i=0}^{43-n}\{\text{pr}(Y = i|x) \times I[\text{pr}(ORR > 0.15|x, Y = i) > 0.85]\},$$

where $\text{pr}(Y = i|x)$ is the probability of observing i responders in future (43-n) participants given *x* out of *n* responders, and $I[\text{pr}(ORR > 0.15|x, Y = i) > 0.85]$=1 if the statement inside [ ] is true; otherwise, the value of I is 0. In summary, the predictive probability in equation (5) can be calculated using the following algorithm:

1) Assign predictive probability *pp* to 0.
2) For *i=0* to *43-n,*
    a. Calculate the posterior probability $ps = \text{pr}(ORR > 0.15|x, Y = i)$ using equation (4).
    b. If *ps >0.85,* do the following:
        i. Calculate the probability of observing $Y = i$ conditional on observing *x* responders using the beta-binomial distribution with parameters *(43-n, x+0.1, n-x+0.9)*, i.e.,

(6) $$\Pr(Y = i|x)$$

$$= \binom{43-n}{i} \frac{B(i+x+0.1, 43-n-i+n-x+0.9)}{B(a,b)}$$

$$= \binom{43-n}{i} \frac{B(i+x+0.1, 43-i-x+0.9)}{B(x+0.1, n-x+0.9)}.$$

ii. Update predictive probability *pp* with *pp*+pr($Y = i|x$).

c. After completing the loop in 2), the final *pp* is the predictive probability of ORR >0.15 with threshold 0.85.

In addition to using the Bayesian approach to calculate the predictive probability of observing a promising ORR, the frequentist approach will also be applied by generating the exact 95% CI of ORR based on the Clopper-Pearson method.

To evaluate the robustness of the observed result, the number of observed responders will be decreased and increased by 1, 2, and 3 (as long as the resulting ORR is between 0 and 100%) to repeat the analyses of ORR.

6. CHANGES TO PLANNED ANALYSES

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

I. PFS-6 was redefined as a survival probability.

II. Definitions and analysis method were added for PFS and OS.

III. The planned informal interim analysis using the Bayesian approach for early futility stopping based on ORR was not performed. Due to this study's rapid enrollment, it was not feasible to perform the planned informal interim analysis using the Bayesian approach because, instead of 10 participants, 53 were enrolled before the one year predicted cutoff time point.

IV. Additional preferred terms were added in electrolyte abnormalities – protocol Section 4.3 vs. SAP section 8.4.1.4.

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8. APPENDICES

8.1. 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).

Time point response: participants with target disease

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.

8.2. FACT/NCCN Ovarian Symptom Index (FOSI) - Version 4

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
O1	I have swelling in my stomach area	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4

Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Subscale	Item Code	Reverse item?		Item response	Item Score
FOSI	GP1	4	-	_____	=_____
	O2	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-32	GP2	4	-	_____	=_____
	O1	4	-	_____	=_____
	GE6	4	-	_____	=_____
	GF7	0	+	_____	=_____
	O3	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 8: _____
Divide by number of items answered: _____**=FOSI total score**

8.3. Mock-up Tables, Listings, and Figure

Mock-up tables, listings and figures are in separate documents.

8.4. Safety Topics of Special Interest Preferred Terms

This appendix outlines the definition of treatment-emergent AESIs. Additional attention will specifically be given to the safety topics of special interest identified using SMQ or customized MedDRA queries based on MedDRA version 27.0.

8.4.1. Protocol-Specified AESIs

Ovarian Toxicity is specified in the protocol as an AESI. However, the majority of participants in this study will not menstruate since they have had their ovaries or uteruses, or both, surgically removed, or were documented to be post-menopausal. Therefore, it will not be relevant to assess ovarian toxicity in this study so the Preferred Terms defining Ovarian Toxicity are not included in this section.

8.4.1.1. Hypersensitivity

The Hypersensitivity search definition is a custom MedDRA version 27.0 query based on selected terms from the Anaphylactic reaction SMQ, Angioedema SMQ, and Allergic conditions High Level Group Term (HLGT). The PTs are listed below, and all will be considered Narrow search terms:

Acquired C1 inhibitor deficiency
AGEP-DRESS overlap
Allergic oedema
Allergic reaction to excipient
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Mouth swelling
Multiple drug hypersensitivity
Oculorespiratory syndrome
Oedema mouth
Orbital oedema

Angioedema	Orbital swelling
Circulatory collapse	Oropharyngeal oedema
Circumoral oedema	Oropharyngeal swelling
Circumoral swelling	Palatal oedema
Conjunctival oedema	Palatal swelling
Corneal oedema	Periorbital oedema
Dermatitis allergic	Periorbital swelling
Dialysis membrane reaction	Pharyngeal oedema
Drug eruption	Pharyngeal swelling
Drug hypersensitivity	Procedural shock
Drug reaction with eosinophilia and systemic symptoms	Scleral oedema
Epiglottic oedema	Severe cutaneous adverse reaction
Erythema multiforme	Shock
Eye oedema	Shock symptom
Eye swelling	SJS-TEN overlap
Eyelid oedema	Stevens-Johnson syndrome
Face oedema	Swelling face
Fixed eruption	Swelling of eyelid
Gingival oedema	Swollen tongue
Gingival swelling	Systemic contact dermatitis
Gleich's syndrome	Tongue oedema
Hereditary angioedema	Toxic epidermal necrolysis
Hereditary angioedema with C1 esterase inhibitor deficiency	Toxic skin eruption
Hereditary angioedema with normal C1 esterase inhibitor	Tracheal oedema
Hypersensitivity	Type I hypersensitivity
Idiopathic angioedema	Type II hypersensitivity

Idiopathic histaminergic angioedema	Type III immune complex mediated reaction
Idiopathic urticaria	Type IV hypersensitivity reaction
Intestinal angioedema	Urticaria
Kounis syndrome	Urticaria cholinergic
Laryngeal oedema	Urticaria chronic
	Urticaria papular

8.4.1.2. Skin Disorder and Rash

The Skin Disorder and Rash search definition is a custom MedDRA version 27.0 query based on selected terms from the Skin and subcutaneous tissue disorders and Infections and infestations System Organ Classes (SOCs). Analyses of skin disorders will be presented for both narrow and broad terms. It is grouped into hidradenitis, skin and subcutaneous rash, and hair follicle subcategories. The PTs are listed below, with Narrow search terms indicated:

Hidradenitis:

Hidradenitis[1]

Sweat gland infection

Abscess sweat gland

Groin sinus excision

Groin abscess

[1] Narrow term.

Skin and subcutaneous rash:

Acne	Rash erythematous[1]
Acne conglobata	Rash follicular[1]
Acne cystic	Rash macular[1]
Acne pustular	Rash maculo-papular[1]
Dermatitis acneiform	Rash maculovesicular

Dermatitis exfoliative	Rash morbilliform[1]
Dermatitis exfoliative generalised	Rash papular[1]
Dermatitis[1]	Rash papulosquamous[1]
Dry skin	Rash pruritic[1]
Erythema[1]	Rash pustular
Erythrodermic atopic dermatitis	Rash rubelliform
Exfoliative rash	Rash scarlatiniform
Mucocutaneous rash	Rash vesicular
Nodular rash[1]	Rash[1]
Pruritus	Skin exfoliation
Pustule	Vasculitic rash

[1] Narrow term.

Hair Follicle:

Abscess of eyelid	Eyelid infection
Acne	Follicular disorder
Acne conglobata	Folliculitis[1]
Acne cosmetica	Folliculitis barbae
Acne cystic	Folliculitis genital
Acne fulminans	Furuncle[1]
Acne infantile	Hordeolum
Acne occupational	Oil acne
Acne varioliformis	Pyoderma
Alopecia areata[1]	Pyoderma streptococcal
Alopecia totalis[1]	Rash pustular[1]
Alopecia universalis[1]	Skin bacterial infection
Alopecia[1]	Staphylococcal skin infection
Carbuncle	Subcutaneous abscess

Dermatitis acneiform

Diffuse alopecia[1]

Eyelid boil

Eyelid folliculitis

[1]Narrow term.

8.4.1.3. Hepatotoxicitiy

The Hepatotoxicity search definition is a custom MedDRA version 27.0 query based on Narrow and Broad terms from the Drug related hepatic disorders - comprehensive search SMQ, Cholestasis and jaundice of hepatic origins SMQ, Drug related hepatic disorders SMQ– severe events only, Liver related investigations, signs and symptoms SMQ, and Liver related coagulation and bleeding disturbances SMQ. The PTs are listed below, with Narrow search terms indicated:

5'nucleotidase increased

Acquired antithrombin III deficiency

Acquired factor IX deficiency

Acquired factor V deficiency[1]

Acquired factor VIII deficiency

Acquired factor XI deficiency

Acquired hepatocerebral degeneration

Acquired protein S deficiency

Acute graft versus host disease in liver

Acute hepatic failure[1]

Acute on chronic liver failure

Acute yellow liver atrophy

Alanine aminotransferase abnormal[1]

Alanine aminotransferase increased[1]

Hepatic hypoperfusion

Hepatic lymphocytic infiltration

Hepatic mass

Hepatic pain

Hepatic sequestration

Hepatic vascular resistance increased

Hepatic venous pressure gradient abnormal

Hepatic venous pressure gradient increased

Hepatobiliary cancer

Hepatobiliary cancer in situ

Hepatobiliary cyst

Hepatobiliary disease

Hepatobiliary neoplasm

Hepatobiliary scan abnormal

Allergic hepatitis
Alloimmune hepatitis
Ammonia abnormal
Ammonia increased
Anorectal varices
Anorectal varices haemorrhage
Anti factor X activity abnormal
Anti factor X activity decreased
Anti factor X activity increased
Anti-liver cytosol antibody type 1 positive[1]
Antithrombin III decreased
Ascites
Aspartate aminotransferase abnormal[1]
Aspartate aminotransferase increased[1]
AST to platelet ratio index increased
AST/ALT ratio abnormal
Asterixis
Autoimmune hepatitis
Bacterascites
Benign hepatic neoplasm
Benign hepatobiliary neoplasm
Bile acids abnormal[1]
Bile acids increased[1]
Bile output abnormal
Bile output decreased
Biliary ascites
Biliary cirrhosis
Hepatoblastoma
Hepatoblastoma recurrent
Hepatocellular carcinoma
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatomegaly
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatosplenomegaly
Hepatotoxicity[1]
Hyperammonaemia
Hyperbilirubinaemia
Hypercholia
Hyperfibrinolysis
Hypertransaminasaemia
Hypoalbuminaemia
Hypocoagulable state
Hypofibrinogenaemia
Hypoprothrombinaemia
Hypothrombinaemia
Hypothromboplastinaemia
Icterus index increased
Immune-mediated cholangitis
Immune-mediated hepatic disorder
Immune-mediated hepatitis
Increased liver stiffness

Biliary fibrosis
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Bilirubin excretion disorder
Bilirubin urine present
Biopsy liver abnormal
Blood alkaline phosphatase abnormal
Blood alkaline phosphatase increased
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Blood cholinesterase abnormal
Blood cholinesterase decreased
Blood fibrinogen abnormal
Blood fibrinogen decreased
Blood thrombin abnormal
Blood thrombin decreased
Blood thromboplastin abnormal
Blood thromboplastin decreased
Bromosulphthalein test abnormal
Cardiohepatic syndrome
Child-Pugh-Turcotte score abnormal
Child-Pugh-Turcotte score increased
Cholaemia
Cholangiosarcoma
Cholestasis
Cholestatic liver injury
International normalised ratio abnormal
International normalised ratio increased
Intestinal varices
Intestinal varices haemorrhage
Intrahepatic portal hepatic venous fistula
Ischaemic hepatitis
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Kayser-Fleischer ring
Leucine aminopeptidase increased
Liver and pancreas transplant rejection
Mixed liver injury
Ocular icterus
Parenteral nutrition associated liver disease
Liver carcinoma ruptured
Liver dialysis
Liver disorder
Liver injury
Liver-kidney microsomal antibody positive[1]
Liver operation
Liver sarcoidosis
Liver transplant
Liver transplant failure
Liver transplant rejection
Lupoid hepatic cirrhosis
Lupus hepatitis

Cholestatic pruritus
Chronic graft versus host disease in liver
Chronic hepatic failure
Chronic hepatitis
Coagulation factor decreased
Coagulation factor IX level abnormal
Coagulation factor IX level decreased
Coagulation factor V level abnormal
Coagulation factor V level decreased
Coagulation factor VII level abnormal
Coagulation factor VII level decreased
Coagulation factor X level abnormal
Coagulation factor X level decreased
Coma hepatic
Complications of transplanted liver
Computerised tomogram liver abnormal
Congestive hepatopathy
Cryptogenic cirrhosis
Cytokeratin 18 increased
Deficiency of bile secretion
Diabetic hepatopathy
Drug-induced liver injury
Duodenal varices
Factor VII activity decreased[1]
Flood syndrome
Focal nodular hyperplasia
Foetor hepaticus
Mixed hepatocellular cholangiocarcinoma
Multivisceral transplantation
Nodular regenerative hyperplasia
Nonalcoholic fatty liver disease
Non-alcoholic steatohepatitis
Non-cirrhotic portal hypertension
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Peripancreatic varices
Peritoneovenous shunt
Portal fibrosis
Portal hypertension
Portal hypertensive colopathy
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal shunt
Portal shunt procedure
Portal tract inflammation
Portal vein cavernous transformation
Portal vein dilatation
Portopulmonary hypertension
Primary biliary cholangitis
Radiation hepatitis
Regenerative siderotic hepatic nodule
Renal and liver transplant
Retrograde portal vein flow

Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gallbladder varices
Gamma-glutamyltransferase abnormal[1]
Gamma-glutamyltransferase increased[1]
Gastric variceal injection
Gastric variceal ligation
Gastric varices
Gastric varices haemorrhage
Gastrooesophageal variceal haemorrhage prophylaxis
Glutamate dehydrogenase increased
Glycocholic acid increased
Graft versus host disease in liver
Granulomatous liver disease
Hepatitis cholestatic
Haemangioma of liver
Haemorrhagic hepatic cyst
Hepatectomy
Hepatic adenoma
Hepatic angiosarcoma
Hepatic atrophy
Hepatic calcification
Hepatic cancer
Hepatic cancer metastatic
Hepatic cancer recurrent
Hepatic cancer stage I
Reye's syndrome
Reynold's syndrome
Small-for-size liver syndrome
Spider naevus
Splenic artery embolisation
Splenic varices
Splenic varices haemorrhage
Splenorenal shunt
Splenorenal shunt procedure
Spontaneous intrahepatic portosystemic venous shunt
Steatohepatitis
Stomal varices
Subacute hepatic failure
Sugiura procedure
Suspected drug-induced liver injury[1]
Transient hepatic attenuation differences
Varices oesophageal
Varicose veins of abdominal wall
White nipple sign
Liver function test abnormal
Liver function test decreased
Liver function test increased
Liver induration
Liver iron concentration abnormal
Liver iron concentration increased
Liver opacity

Hepatic cancer stage II	Liver palpable
Hepatic cancer stage III	Liver scan abnormal
Hepatic cancer stage IV	Liver tenderness
Hepatic cirrhosis	Magnetic resonance imaging hepatobiliary abnormal
Hepatic cyst	Magnetic resonance proton density fat fraction measurement
Hepatic cyst ruptured	Mitochondrial aspartate aminotransferase increased
Hepatic cytolysis	Model for end stage liver disease score abnormal
Hepatic encephalopathy	Model for end stage liver disease score increased
Hepatic encephalopathy prophylaxis	Molar ratio of total branched-chain amino acid to tyrosine
Hepatic failure	Osteopontin increased
Hepatic fibrosis	Perihepatic discomfort
Hepatic haemangioma rupture	Periportal oedema
Hepatic hamartoma	Peritoneal fluid protein abnormal
Hepatic hydrothorax	Peritoneal fluid protein decreased
Hepatic infiltration eosinophilic	Peritoneal fluid protein increased
Hepatic lesion	Pneumobilia
Hepatic necrosis	Portal vein flow decreased
Hepatic neoplasm	Portal vein pressure increased
Hepatic perfusion disorder	Retinol binding protein decreased
Hepatic steato-fibrosis	Transaminases abnormal[1]
Hepatic steatosis	Transaminases increased[1]
Hepatitis	Ultrasound liver abnormal
Hepatitis acute	Urine bilirubin increased

Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis toxic[1]
Guanase increased
Haemorrhagic ascites
Hepaplastin abnormal
Hepaplastin decreased
Hepatic artery flow decreased
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic fibrosis marker abnormal
Hepatic fibrosis marker increased
Hepatic function abnormal
Hepatic hypertrophy
Urobilinogen urine decreased
Urobilinogen urine increased
X-ray hepatobiliary abnormal
Protein C decreased
Protein S abnormal
Protein S decreased
Prothrombin level abnormal
Prothrombin level decreased
Prothrombin time abnormal
Prothrombin time prolonged
Prothrombin time ratio abnormal
Prothrombin time ratio increased

[1]Narrow term.

8.4.1.4. Electrolyte Disorder

Selected treatment-emergent abnormally low electrolyte disorder adverse events will be summarized. The electrolyte disorder search definition is a custom MedDRA version 27.0 query based on selected terms from the Metabolism and nutrition disorders and Investigations SOCs. The PTs are as defined below for each electrolyte. The frequency table will be summarized by descending frequency of lab analyte and PT. A shift table will be generated for lab grades in hypocalcemia, hypercalcemia, hypomagnesemia, hypermagnesemia, hypokalemia, hyperkalemia, hyponatremia, and hypernatremia, as well as for clinical categorization in phosphate.

Lab Analyte	Pertinent PTs
Hypocalcemia:	Blood calcium decreased, Hypocalcaemia, Hypocalcaemic seizure
Hypomagnesaemia:	Blood magnesium decreased, Hypomagnesaemia
Hypophosphatemia:	Blood phosphorus decreased, Hypophosphataemia
Hypokalaemia:	Blood potassium decreased, Hypokalaemia, Hypokalaemic syndrome
Hyponatremia:	Blood sodium decreased, Hyponatraemia, Hyponatraemic coma, Hyponatraemic encephalopathy, Hyponatraemic seizure, Hyponatraemic syndrome

8.4.1.5. Non-Melanoma Skin Cancers

The non-melanoma skin cancers search definition is a custom MedDRA version 27.0 query based on selected terms from the Skin neoplasms malignant and unspecified (excluding melanoma) HLT within the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC, plus the PT of Squamous cell carcinoma. The PTs are shown below:

Atypical fibroxanthoma	Neoplasm skin
Basal cell carcinoma	Neuroendocrine carcinoma of the skin
Basal cell carcinoma metastatic	Pilomatrix carcinoma
Basal cell naevus syndrome	Porocarcinoma
Basosquamous carcinoma of skin	Primary cutaneous adenoid cystic carcinoma
Bowen's disease	Sebaceous carcinoma
Carcinoma in situ of skin	Squamoproliferative lesion
Dysplastic naevus syndrome	Skin angiosarcoma
Eccrine carcinoma	Skin cancer
Epidermal naevus syndrome	Skin cancer metastatic
Keratoacanthoma	Skin neoplasm bleeding
Malignant sweat gland neoplasm	Skin squamous cell carcinoma metastatic

Marjolin's ulcer	Skin squamous cell carcinoma recurrent
Mastocytoma	Squamous cell carcinoma of skin
	Trichoblastic carcinoma
	Squamous cell carcinoma

8.4.2. Other Safety Topics of Special Interest

Safety topics of special interest have been identified based on the review of safety data from prior studies with nirogacestat and include additional AEs beyond those specified in Protocol Section 11.3.1 as AESIs. These safety topics of interest are defined for analysis purposes by using standardized MedDRA queries (SMQ) or customized MedDRA queries, as described below.

8.4.2.1. Musculoskeletal Disorders

The Musculoskeletal Disorders search definition is a custom MedDRA version 27.0 query based on selected terms from the Bone disorders (excluding congenital and fractures) HLGT. The PTs are shown below:

Bone atrophy	Fracture delayed union
Bone callus excessive	Fracture malunion
Bone decalcification	Fracture nonunion
Bone erosion	Idiopathic juvenile osteoporosis
Bone demineralisation	Melorheostosis
Bone formation decreased	Osteodystrophy
Bone formation increased	Osteolysis
Bone hypertrophy	Osteomalacia
Bone loss	Osteopenia
Bone pain	Osteoporosis
Callus formation delayed	Osteoporosis circumscripta cranii
Enostosis	Osteoporosis postmenopausal

Exostosis	Osteosclerosis
Exostosis of external ear canal	Osteosis
Exostosis of jaw	Resorption bone decreased
Extraskeletal ossification	Resorption bone increased

8.4.2.2. Bone Fracture

The Bone Fracture search definition is a custom MedDRA version 27.0 query based on selected terms from the Fractures of the Musculoskeletal HLGT and Connective tissue disorders SOC. The PTs are shown below:

Acetabulum fracture	Impacted fracture
Ankle fracture	Jaw fracture
Atypical femur fracture	Limb fracture
Atypical fracture	Lisfranc fracture
Avulsion fracture	Lower limb fracture
Bone fissure	Lumbar vertebral fracture
Bone fragmentation	Maisonneuve fracture
Cervical vertebral fracture	Metaphyseal corner fracture
Chance fracture	Multiple fractures
Clavicle fracture	Neurogenic fracture
Comminuted fracture	Open fracture
Complicated fracture	Osteochondral fracture
Compression fracture	Osteo-meningeal breaches
Costal cartilage fracture	Osteophyte fracture
Craniofacial fracture	Osteoporotic fracture
Craniofacial injury	Patella fracture
Epiphyseal fracture	Pathological fracture
Facial bones fracture	Pelvic fracture

Femoral neck fracture
Femur fracture
Fibula fracture
Flail chest
Foot fracture
Forearm fracture
Fracture
Fracture blisters
Fracture delayed union
Fracture displacement
Fracture infection
Fracture malunion
Fracture nonunion
Fracture of clavicle due to birth trauma
Fractured coccyx
Fractured sacrum
Fractured skull depressed
Greenstick fracture
Hand fracture
Hip fracture
Humerus fracture
Ilium fracture
Periprosthetic fracture
Pseudarthrosis
Pseudofracture
Radius fracture
Rib fracture
Sacroiliac fracture
Scapula fracture
Scapulothoracic dissociation
Skull fracture
Skull fractured base
Spinal compression fracture
Spinal fracture
Spinal fusion fracture
Sternal fracture
Stress fracture
Subchondral insufficiency fracture
Thoracic vertebral fracture
Tibia fracture
Torus fracture
Traumatic fracture
Ulna fracture
Upper limb fracture
Wrist fracture

8.4.2.3. Mucositis/Stomatitis

The Mucositis/Stomatitis search definition is a custom MedDRA version 27.0 query based on selected terms from the Stomatitis and ulceration and Oral soft tissue signs and symptoms HLTs. The PTs are shown below:

Mouth ulceration	Palatal ulcer
Oral mucosa erosion	Stomatitis haemorrhagic
Oral pain	Stomatitis necrotizing
Oropharyngeal pain	Stomatitis

8.4.2.4. Hematologic Disorders

The Hematologic Disorders search definition is a custom MedDRA version 27.0 query based on selected terms from the Blood and lymphatic disorders SOC. The PTs are shown below:

Agranulocytosis	Lymphocyte percentage decreased
Anaemia	Lymphocytopenia neonatal
Anaemia macrocytic	Lymphopenia
Anaemia neonatal	Metamyelocyte count decreased
Aplasia pure red cell	Microcytic anaemia
Aplastic anaemia	Monoblast count decreased
Band neutrophil count decreased	Monocyte count abnormal
Band neutrophil percentage decreased	Monocyte count decreased
Basophil count abnormal	Monocyte percentage decreased
Basophil count decreased	Monocytopenia
Basophil percentage decreased	Mononuclear cell count decreased
Basophilopenia	Myeloblast count decreased
B-lymphocyte abnormalities	Myeloblast percentage decreased
B-lymphocyte count abnormal	Myelocyte count decreased
B-lymphocyte count decreased	Myelocyte percentage decreased
Cyclic neutropenia	Myeloid maturation arrest

Differential white blood cell count abnormal	Neutropenia
Eosinopenia	Neutropenia neonatal
Eosinophil count abnormal	Neutropenic infection
Eosinophil count decreased	Neutropenic sepsis
Eosinophil percentage decreased	Neutrophil count abnormal
Erythroblast count abnormal	Neutrophil count decreased
Erythroblast count decreased	Neutrophil percentage decreased
Erythroid maturation arrest	Normochromic anaemia
Erythropenia	Normochromic normocytic anaemia
Erythropoiesis abnormal	Normocytic anaemia
Febrile neutropenia	Plasma cell disorder
Foetal anaemia	Plasma cells absent
Full blood count abnormal	Proerythroblast count abnormal
Granulocyte count decreased	Proerythroblast count decreased
Granulocytes abnormal	Promyelocyte count decreased
Granulocytes maturation arrest	Pure white cell aplasia
Granulocytopenia	Radiation leukopenia
Granulocytopenia neonatal	Red blood cell count abnormal
Haematocrit abnormal	Red blood cell count decreased
Haematocrit decreased	Reticulocyte count abnormal
Haemoglobin abnormal	Reticulocyte count decreased
Haemoglobin decreased	Reticulocyte percentage decreased
Hypohaemoglobinaemia	Reticulocytopenia
Hypoplastic anaemia	T-lymphocyte count abnormal
Idiopathic neutropenia	T-lymphocyte count abnormal
Leukoerythroblastic anaemia	T-lymphocyte count decreased

Leukopenia	White blood cell analysis abnormal
Leukopenia neonatal	White blood cell count abnormal
Lymphocyte count abnormal	White blood cell count decreased
Lymphocyte count decreased	White blood cell disorder
Lymphocyte percentage abnormal	

8.4.2.5. Opportunistic Infections

The Opportunistic Infections search definition is based on MedDRA version 27.0 Narrow and Broad terms from the Opportunistic Infections SMQ. The PTs are shown below, with Narrow search terms indicated:

Abdominal sepsis	Human herpesvirus 6 infection reactivation[1]
Abiotrophia defectiva endocarditis[1]	Human herpesvirus 6 viraemia[1]
Abscess fungal	Human herpesvirus 7 infection
Acanthamoeba infection	Human herpesvirus 8 infection[1]
Achromobacter infection	Human metapneumovirus test positive
Acid fast bacilli infection[1]	Human papilloma virus test positive
Acinetobacter bacteraemia	Human polyomavirus infection
	Hyperparasitaemia[1]
Acinetobacter infection	Immune reconstitution inflammatory syndrome
Acinetobacter sepsis[1]	Immune reconstitution inflammatory syndrome associated tuberculosis[1]
Actinomyces test positive	Indeterminate leprosy[1]
	Indeterminate tuberculosis test
Actinomycosis	Infection in an immunocompromised host[1]
Actinomycotic abdominal infection	Infection susceptibility increased[1]
Actinomycotic pulmonary infection	Infectious thyroiditis
Actinomycotic sepsis[1]	Infective aneurysm

Actinomycotic skin infection	Influenza
Acute haemorrhagic conjunctivitis	Influenza A virus test positive
Acute hepatitis B	Influenza B virus test positive
Acute hepatitis C	Influenza C virus test positive
	Influenza myocarditis
Acute pulmonary histoplasmosis[1]	Influenza virus test positive
Adenoviral conjunctivitis	Interferon gamma release assay positive
Adenoviral encephalitis[1]	Intestinal tuberculosis[1]
Adenoviral haemorrhagic cystitis[1]	Isosporiasis[1]
	Jamestown Canyon encephalitis
Adenoviral hepatitis	JC polyomavirus test positive
Adenoviral meningitis[1]	JC virus CSF test positive[1]
Adenoviral upper respiratory infection	JC virus granule cell neuronopathy[1]
Adenovirus encephalomyeloradiculitis[1]	JC virus infection[1]
Adenovirus infection	Joint tuberculosis[1]
Adenovirus interstitial nephritis[1]	
Adenovirus test positive	Kaposi's sarcoma[1]
Adrenal gland tuberculosis[1]	Kaposi's sarcoma AIDS related[1]
Aerococcus urinae infection	Keratitis fungal
Aeromonas infection	Keratitis viral
Aeromonas test positive	Klebsiella bacteraemia
African trypanosomiasis	Klebsiella infection
	Klebsiella pneumoniae invasive syndrome
Alcaligenes infection	Klebsiella sepsis
Algid malaria	
Allergic bronchopulmonary mycosis	Klebsiella test positive

	Lactobacillus bacteraemia
Allescheriosis	Lactobacillus infection
Alpha haemolytic streptococcal infection	Laryngeal cryptococcosis[1]
Alphavirus test positive	Laryngitis fungal[1]
	Leclercia bacteraemia[1]
Alternaria infection[1]	Legionella infection
American trypanosomiasis	Legionella test positive
Amoeba test positive	Leishmaniasis
Amoebiasis	Lepromatous leprosy[1]
Amoebic brain abscess[1]	Leprosy[1]
Amoebic colitis	Leptotrichia infection
Amoebic dysentery	Leuconostoc infection
Amoebic lung abscess[1]	Listeria encephalitis[1]
Amoebic skin ulcer	Listeria sepsis[1]
Amoeboma[1]	
Anal candidiasis	Listeria test positive
Anal fungal infection	Listeriosis[1]
Angina gangrenous	Lower respiratory tract herpes infection[1]
Angiostrongylus infection	Lower respiratory tract infection fungal[1]
Anogenital warts	Lower respiratory tract infection viral
Anorectal human papilloma virus infection	Lupus vulgaris[1]
Anthrax sepsis	Lymph node tuberculosis[1]
Anti-JC virus antibody index	Lymphadenitis fungal[1]
Arbovirus test positive	Malaria
Arenavirus test positive	Malaria antibody test positive
Arthritis fungal[1]	Malarial myocarditis

Arthritis salmonella	Male genital tract tuberculosis[1]
Arthritis-dermatitis syndrome	
Aspergilloma	Mammary tuberculosis[1]
Aspergillosis oral[1]	Mastitis fungal[1]
	Mastoiditis fungal
Aspergillus infection[1]	Measles meningitis
Aspergillus test positive	Meningitis aspergillus[1]
Atypical mycobacterial infection[1]	Meningitis candida[1]
Atypical mycobacterial lower respiratory tract infection[1]	Meningitis coccidioides[1]
Atypical mycobacterial lymphadenitis[1]	Meningitis cronobacter
Atypical mycobacterial pneumonia[1]	Meningitis cryptococcal[1]
Atypical mycobacterium pericarditis[1]	Meningitis enterococcal
Atypical mycobacterium test positive	Meningitis exserohilum[1]
Atypical pneumonia	Meningitis fungal[1]
Avian influenza	Meningitis haemophilus
Babesiosis	Meningitis herpes[1]
Bacillary angiomatosis[1]	Meningitis histoplasma[1]
Bacteraemia	Meningitis listeria[1]
Bacterial myositis	Meningitis meningococcal
Bacterial sepsis	Meningitis pneumococcal
Bacterial test positive	Meningitis salmonella
Balamuthia infection	Meningitis staphylococcal
Balanitis candida	Meningitis streptococcal
Bartonella test positive	Meningitis toxoplasmal[1]
Bartonellosis	Meningitis trypanosomal

Beta haemolytic streptococcal infection	Meningitis tuberculous[1]
Biliary sepsis	Meningoencephalitis herpes simplex neonatal
Biliary tract infection cryptosporidial[1]	
Biliary tract infection fungal[1]	Meningoencephalitis viral
BK polyomavirus test positive	Meningomyelitis herpes[1]
BK virus infection[1]	Merkel cell polyomavirus infection
Bladder candidiasis	MERS-CoV test positive
Blastocystis infection[1]	Metapneumovirus bronchiolitis
Blastomycosis[1]	Metapneumovirus infection
Blood beta-D-glucan abnormal	Metapneumovirus pneumonia
Blood beta-D-glucan increased	Methylobacterium infection[1]
Blood beta-D-glucan positive	Micrococcal sepsis
Blood culture positive	Micrococcus infection
Body tinea	Micrococcus test positive
Bone tuberculosis[1]	Microsporidia infection[1]
Borderline leprosy[1]	Microsporum infection
Botryomycosis	Middle East respiratory syndrome
Bovine tuberculosis[1]	Miliary pneumonia[1]
Breakthrough COVID-19	
Bronchitis fungal[1]	Morganella infection
Bronchitis haemophilus	Mucocutaneous candidiasis
Bronchopulmonary aspergillosis[1]	Mucormycosis[1]
	Multisystem inflammatory syndrome in adults
Bronchopulmonary aspergillosis allergic	Multisystem inflammatory syndrome in children
Brucella sepsis	Mumps antibody test positive
Brucella test positive	Murray Valley encephalitis

Bullous impetigo	Mycetoma mycotic[1]
Burkholderia cepacia complex infection	Mycobacterial infection[1]
Burkholderia cepacia complex sepsis[1]	Mycobacterial peritonitis[1]
Burkholderia gladioli infection[1]	Mycobacterium abscessus infection[1]
Burkholderia infection	Mycobacterium avium complex immune restoration disease[1]
Burkholderia mallei infection	Mycobacterium avium complex infection[1]
Burkholderia pseudomallei infection[1]	Mycobacterium chelonae infection[1]
Burkholderia test positive	Mycobacterium fortuitum infection[1]
Bursitis infective staphylococcal	Mycobacterium kansasii infection[1]
Buschke-Lowenstein's tumour	Mycobacterium leprae test positive
Cache Valley virus infection	
Campylobacter bacteraemia	
Campylobacter sepsis	Mycobacterium marinum infection[1]
Campylobacter test positive	Mycobacterium test positive
Candida cervicitis	Mycobacterium tuberculosis complex test positive
Candida endophthalmitis[1]	Mycobacterium ulcerans infection[1]
Candida infection	Mycotic corneal ulcer
Candida osteomyelitis[1]	Mycotic endophthalmitis[1]
Candida pneumonia[1]	Mycotoxicosis
Candida retinitis[1]	Myocarditis mycotic[1]
Candida sepsis[1]	Myocarditis septic
Candida test positive	Myocarditis toxoplasmal[1]
Candidiasis of trachea[1]	Nail candida
Capnocytophaga infection[1]	Nasal candidiasis
Capnocytophaga sepsis[1]	Nasal herpes
Capnocytophaga test positive	Necrotising fasciitis fungal[1]

Capripox viral infection	
Cardiac tuberculosis[1]	
Cat scratch disease	Necrotising fasciitis staphylococcal
Cellulitis enterococcal	Necrotising fasciitis streptococcal
Cellulitis pasteurella	Necrotising herpetic retinopathy[1]
Cellulitis staphylococcal	Neisseria test positive
	Neonatal bacteraemia
Cellulitis streptococcal	Neonatal candida infection
Central nervous system fungal infection[1]	Neonatal infective mastitis
Central nervous system listeria infection[1]	
Central nervous system viral infection[1]	Neonatal mucocutaneous herpes simplex
Cerebral aspergillosis[1]	Neurocryptococcosis[1]
Cerebral fungal infection[1]	Neutropenic infection
Cerebral malaria	Neutropenic sepsis[1]
Cerebral nocardiosis[1]	
Cerebral toxoplasmosis[1]	Nocardia sepsis[1]
Cervicitis human papilloma virus	Nocardia test positive
Cervicitis streptococcal	Nocardiosis[1]
Cervix warts	Oesophageal candidiasis[1]
Chagas' cardiomyopathy	
Chagas' gastrointestinal disease	
Chancroid	Oesophageal tuberculosis[1]
Chlamydia test positive	Onychomycosis
Choriomeningitis lymphocytic	Ophthalmic herpes simplex[1]
Choroid tubercles[1]	Ophthalmic herpes zoster[1]

Chromoblastomycosis[1]	Opportunistic infection[1]
Chronic active Epstein-Barr virus infection	Oral candidiasis
Chronic hepatitis B	Oral fungal infection
Chronic hepatitis C	Oral hairy leukoplakia
Chronic hyperplastic candidiasis[1]	
Chronic pulmonary histoplasmosis[1]	Oral herpes
	Oral herpes zoster
Citrobacter infection	Oral tuberculosis[1]
Citrobacter sepsis	Organic dust toxic syndrome
Citrobacter test positive	Oro-pharyngeal aspergillosis[1]
Clostridial sepsis	Oropharyngeal candidiasis
Clostridium bacteraemia	Oropharyngitis fungal
Clostridium colitis	Orthopox virus infection
Clostridium difficile colitis	Orthopoxvirus test positive
	Osteoarticular sporotrichosis[1]
Clostridium difficile infection	Osteomyelitis blastomyces[1]
Clostridium test positive	Osteomyelitis fungal[1]
Coccidioides encephalitis[1]	Osteomyelitis salmonella
Coccidioidomycosis[1]	Otitis externa candida
Colitis herpes[1]	Otitis media fungal[1]
Complicated malaria[1]	
Conjunctivitis tuberculous[1]	Otitis media haemophilus
Coronavirus infection	
Coronavirus pneumonia	
Coronavirus test positive	Pancreatitis fungal[1]
Corynebacterium infection	Pantoea agglomerans infection

Corynebacterium sepsis	Pantoea agglomerans test positive
Corynebacterium test positive	Papilloma viral infection
COVID-19	Paracoccidioides infection[1]
COVID-19 pneumonia	Parainfluenzae viral bronchitis
Coxiella infection	Parainfluenzae viral laryngotracheobronchitis
Coxiella test positive	Parainfluenzae virus infection
Coxsackie viral disease of the newborn	Parapharyngeal space infection
Creutzfeldt-Jakob disease	Parasitic encephalitis
Cronobacter bacteraemia	Parechovirus infection
Cronobacter infection	Parvovirus B19 infection reactivation[1]
Cronobacter necrotising enterocolitis	Pasteurella test positive
Cryptococcal cutaneous infection[1]	Peliosis hepatis
Cryptococcal fungaemia[1]	Pelvic sepsis
Cryptococcal meningoencephalitis[1]	Penicillium infection[1]
Cryptococcosis[1]	Penile gangrene
Cryptococcus test positive	Penile wart
Cryptosporidiosis infection[1]	Peptostreptococcus infection
CSF measles antibody positive	Peptostreptococcus test positive
Cutaneous anthrax	Perianal streptococcal infection
Cutaneous coccidioidomycosis[1]	Pericarditis fungal[1]
Cutaneous mucormycosis	Pericarditis histoplasma[1]
Cutaneous sporotrichosis	Pericarditis tuberculous[1]
Cutaneous tuberculosis[1]	Perinatal HBV infection
Cyclosporidium infection	Periporitis staphylogenes
Cystitis escherichia	Peritoneal candidiasis[1]
Cystitis klebsiella	Peritoneal tuberculosis[1]

Cystitis pseudomonal	Peritonitis pneumococcal
Cytomegalovirus chorioretinitis[1]	Phaeohyphomycosis[1]
Cytomegalovirus colitis[1]	Pharyngeal abscess
Cytomegalovirus duodenitis[1]	Pharyngoconjunctival fever of children
Cytomegalovirus enteritis[1]	Plasmodium falciparum infection
Cytomegalovirus enterocolitis[1]	Plasmodium malariae infection
Cytomegalovirus gastritis[1]	Plasmodium ovale infection
Cytomegalovirus gastroenteritis[1]	Plasmodium vivax infection
	Plesiomonas shigelloides infection
Cytomegalovirus gastrointestinal infection[1]	Pneumococcal bacteraemia
Cytomegalovirus gastrointestinal ulcer[1]	Pneumococcal infection
Cytomegalovirus hepatitis[1]	Pneumococcal sepsis
Cytomegalovirus immunisation	Pneumocystis jirovecii infection[1]
Cytomegalovirus infection[1]	Pneumocystis jirovecii pneumonia[1]
Cytomegalovirus infection reactivation[1]	Pneumocystis test positive
Cytomegalovirus mononucleosis[1]	Pneumonia adenoviral
Cytomegalovirus mucocutaneous ulcer[1]	Pneumonia anthrax
Cytomegalovirus myelomeningoradiculitis[1]	
Cytomegalovirus myocarditis[1]	Pneumonia cryptococcal[1]
Cytomegalovirus oesophagitis[1]	Pneumonia cytomegaloviral[1]
Cytomegalovirus pancreatitis[1]	Pneumonia escherichia
Cytomegalovirus pericarditis[1]	Pneumonia fungal[1]
Cytomegalovirus syndrome[1]	Pneumonia haemophilus
Cytomegalovirus test positive	Pneumonia herpes viral[1]

Cytomegalovirus urinary tract infection[1]	Pneumonia influenzal
Cytomegalovirus viraemia[1]	Pneumonia Klebsiella
Delftia acidovorans infection	Pneumonia legionella[1]
Deltaretrovirus test positive	Pneumonia measles
Dengue fever	Pneumonia parainfluenzae viral
Dengue shock syndrome	
Dental sepsis	
Dermatolymphangioadenitis	
Device related bacteraemia	Pneumonia pneumococcal
Device related fungaemia	
Device related sepsis	Pneumonia pseudomonal
Disseminated aspergillosis[1]	Pneumonia respiratory syncytial viral
Disseminated blastomycosis[1]	Pneumonia salmonella
Disseminated coccidioidomycosis[1]	Pneumonia staphylococcal
Disseminated cryptococcosis[1]	Pneumonia streptococcal
Disseminated cytomegaloviral infection[1]	Pneumonia toxoplasmal[1]
Disseminated enteroviral infection[1]	
Disseminated gonococcal infection	
Disseminated herpes simplex	
Disseminated leishmaniasis[1]	Polyomavirus test positive
Disseminated mucormycosis[1]	Polyomavirus viraemia[1]
Disseminated mycobacterium avium complex infection[1]	Polyomavirus-associated nephropathy1
Disseminated paracoccidioidomycosis[1]	Pontiac fever
	Porphyromonas bacteraemia

Disseminated sporotrichosis[1]	Porphyromonas infection
Disseminated strongyloidiasis[1]	Porphyromonas test positive
Disseminated toxoplasmosis[1]	Post streptococcal glomerulonephritis
Disseminated trichosporonosis[1]	Post transplant lymphoproliferative disorder
Disseminated tuberculosis[1]	Presumed ocular histoplasmosis syndrome
Disseminated varicella[1]	Prion agent test positive
Disseminated varicella zoster vaccine virus infection[1]	Proctitis fungal
Disseminated varicella zoster virus infection[1]	Proctitis herpes[1]
Ear infection fungal	Proctitis monilial
Ear tuberculosis[1]	Progressive multifocal leukoencephalopathy[1]
Eczema herpeticum	Progressive vaccinia[1]
Elsberg syndrome[1]	
Encephalitis australia	Prostatitis Escherichia coli
Encephalitis california	Prostatitis tuberculous[1]
Encephalitis cytomegalovirus[1]	Protothecosis[1]
Encephalitis eastern equine	Pseudallescheria infection[1]
Encephalitis enteroviral	Pseudallescheria sepsis[1]
Encephalitis fungal[1]	Pseudoaneurysm infection
Encephalitis herpes[1]	
Encephalitis influenzal	Pseudomonal bacteraemia
Encephalitis Japanese B	Pseudomonal sepsis
Encephalitis meningococcal	Pseudomonas aeruginosa meningitis[1]
Encephalitis mumps	Pseudomonas bronchitis
Encephalitis post varicella[1]	Pseudomonas infection
Encephalitis protozoal	Pseudomonas peritonitis
Encephalitis rickettsial	Pseudomonas test positive

	Pulmonary blastomycosis[1]
	Pulmonary gangrene
	Pulmonary histoplasmosis[1]
Encephalitis venezuelan equine	Pulmonary mucormycosis[1]
Encephalitis viral	Pulmonary nocardiosis[1]
Encephalitis western equine	Pulmonary sepsis
Encephalomyelitis rubella	Pulmonary trichosporonosis[1]
Endocarditis candida[1]	Pulmonary tuberculoma[1]
Endocarditis enterococcal	Pulmonary tuberculosis[1]
Endocarditis haemophilus	Pyelonephritis fungal[1]
Endocarditis histoplasma[1]	Pyoderma streptococcal
Endocarditis pseudomonal	Pythium insidiosum infection
Endocarditis Q fever[1]	Q fever
Endocarditis staphylococcal	Raoultella ornithinolytica infection
Endocarditis viral	Renal tuberculosis[1]
Enterobacter bacteraemia	Respiratory moniliasis
Enterobacter infection	Respiratory syncytial virus bronchiolitis
Enterobacter pneumonia	Respiratory syncytial virus bronchitis
Enterobacter sepsis	Respiratory syncytial virus infection
Enterobacter test positive	Respiratory syncytial virus test positive
Enterobacter tracheobronchitis	Respiratory tract infection fungal[1]
Enterococcal bacteraemia	Retinitis histoplasma[1]
Enterococcal infection	Retinitis viral[1]
Enterococcal sepsis	Retroviral rebound syndrome
Enterococcus test positive	Rhinocerebral mucormycosis[1]
	Rhizobium radiobacter bacteraemia[1]
Enterocolitis fungal[1]	Rhodococcus infection[1]

Enterocolitis viral	Rhodococcus test positive
Enterovirus test positive	Roseolovirus test positive
Epididymitis blastomyces[1]	Rubella antibody positive
Epididymitis tuberculous[1]	Salmonella bacteraemia
Epiglottitis haemophilus	Salmonella sepsis
Epstein-Barr viraemia	Salmonella test positive
Epstein-Barr virus antibody positive	Salmonellosis
Epstein-Barr virus antigen positive	Salpingitis tuberculous[1]
Epstein-Barr virus associated lymphoma	SARS-CoV-1 test positive
Epstein-Barr virus associated lymphoproliferative disorder[1]	SARS-CoV-2 antibody test positive
Epstein-Barr virus infection	SARS-CoV-2 sepsis
Epstein-Barr virus infection reactivation[1]	SARS-CoV-2 test false negative
Epstein-Barr virus test positive	SARS-CoV-2 test positive
Erysipelas	Scarlet fever
Erythema induratum	Scedosporium infection[1]
Escherichia bacteraemia	Sepsis
Escherichia infection	Sepsis neonatal
Escherichia sepsis	Sepsis pasteurella
Escherichia test positive	Sepsis syndrome
Escherichia urinary tract infection	Septic arthritis haemophilus
Escherichia vaginitis	Septic arthritis staphylococcal[1]
Exanthema subitum	Septic arthritis streptobacillus
Exserohilum infection[1]	Septic arthritis streptococcal
	Septic cardiomyopathy
	Septic cerebral embolism

Exserohilum test positive	Septic coagulopathy
Extrapulmonary tuberculosis[1]	Septic embolus
	Septic endocarditis
Eye infection fungal	Septic necrosis
Eye infection staphylococcal	Septic phlebitis
Eye infection toxoplasmal[1]	Septic pulmonary embolism
Eye infection viral	Septic shock
Female genital tract tuberculosis[1]	Serratia bacteraemia
Flavivirus test positive	Serratia infection
Flavobacterium infection[1]	Serratia sepsis
Flavobacterium test positive	Serratia test positive
Fournier's gangrene[1]	Severe acute respiratory syndrome
Fungaemia[1]	Severe invasive streptococcal infection
Fungal abscess central nervous system[1]	Shewanella algae bacteraemia
Fungal cystitis	Shigella infection
Fungal endocarditis[1]	Shigella test positive
Fungal infection	Silicotuberculosis
Fungal labyrinthitis[1]	Sinusitis aspergillus[1]
Fungal myositis[1]	
Fungal oesophagitis[1]	Sinusitis fungal[1]
Fungal paronychia	Skin candida
Fungal peritonitis[1]	Sphingomonas paucimobilis bacteraemia[1]
Fungal retinitis[1]	Sphingomonas paucimobilis infection[1]
Fungal rhinitis[1]	Spleen tuberculosis[1]
Fungal sepsis[1]	Splenic candidiasis[1]
Fungal test positive	Splenic infection fungal[1]

Fungal tracheitis[1]	Sporotrichosis
Fusarium endocarditis[1]	
Fusarium infection[1]	Spotted fever rickettsia test positive
Gastric ulcer helicobacter	St. Louis encephalitis
Gastritis fungal[1]	Staphylococcal abscess
Gastritis herpes[1]	Staphylococcal bacteraemia
Gastroenteritis adenovirus	Staphylococcal impetigo
Gastroenteritis aeromonas	Staphylococcal infection
Gastroenteritis cryptococcal[1]	Staphylococcal mediastinitis
Gastroenteritis cryptosporidial[1]	Staphylococcal osteomyelitis
Gastroenteritis Escherichia coli	Staphylococcal scalded skin syndrome
Gastroenteritis pseudomonas	Staphylococcal sepsis
Gastroenteritis salmonella	Staphylococcal skin infection
Gastroenteritis staphylococcal	Staphylococcal toxaemia
Gastroenteritis vibrio	Staphylococcus test positive
Gastrointestinal anthrax	Stenotrophomonas bacteraemia[1]
Gastrointestinal candidiasis	Stenotrophomonas infection[1]
	Stenotrophomonas maltophilia pneumonia[1]
Gastrointestinal fungal infection[1]	Stenotrophomonas sepsis[1]
Gastrointestinal mucormycosis[1]	Stenotrophomonas test positive
Genital candidiasis	Stoma site candida
Genital herpes	Stomatococcal infection
Genital herpes simplex	Stomatococcus test positive
Genital herpes zoster	Streptobacillary fever
Genital infection fungal	Streptobacillus infection
Geotrichum infection	Streptobacillus test positive
Group B streptococcus neonatal sepsis	Streptococcal abscess

H1N1 influenza	Streptococcal bacteraemia
Haematological infection	
Haemophilus bacteraemia	Streptococcal bronchitis
Haemophilus infection	Streptococcal endocarditis
Haemophilus sepsis	Streptococcal impetigo
Haemophilus test positive	Streptococcal infection
Helicobacter gastritis	Streptococcal sepsis
Helicobacter infection	Streptococcal urinary tract infection
Helicobacter sepsis	Streptococcus test positive
Helicobacter test positive	Streptokinase antibody increased
Hepatic actinomycosis[1]	
Hepatic candidiasis[1]	Strongyloidiasis
Hepatic infection fungal[1]	Subacute sclerosing panencephalitis
	Submandibular abscess
Hepatitis A antibody abnormal	Superinfection fungal[1]
Hepatitis A antibody positive	Superinfection mycobacterial[1]
Hepatitis A antigen positive	Suspected COVID-19
Hepatitis A virus test positive	Syphilis
	Syphilitic pelvic inflammatory disease[1]
Hepatitis B	Systemic candida[1]
Hepatitis B antibody abnormal	Systemic inflammatory response syndrome
Hepatitis B antibody positive	Systemic mycosis[1]
Hepatitis B antigen positive	Thrombophlebitis septic
Hepatitis B core antibody positive	Thyroid tuberculosis[1]
Hepatitis B core antigen positive	Tick-borne viral encephalitis
Hepatitis B DNA assay positive	Tonsillitis fungal[1]
Hepatitis B DNA increased	Torulopsis infection

Hepatitis B e antibody positive
Hepatitis B e antigen positive
Hepatitis B surface antibody positive
Hepatitis B surface antigen positive
Hepatitis B virus test positive
Hepatitis C
Hepatitis C antibody positive
Hepatitis C core antibody positive
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C virus test positive
Hepatitis D
Hepatitis D antibody positive
Hepatitis D antigen positive
Hepatitis D RNA positive
Hepatitis D virus test positive
Hepatitis E antibody positive
Hepatitis E antigen positive
Hepatitis E virus test positive
Hepatitis infectious mononucleosis
Hepatitis non-A non-B
Hepatitis non-A non-B non-C
Hepatitis syphilitic
Hepatitis toxoplasmal
Hepatitis viral test positive
Toxic shock syndrome staphylococcal
Toxic shock syndrome streptococcal
Toxoplasma serology positive
Toxoplasmosis[1]
Toxoplasmosis prophylaxis
Treponema test positive
Trichophytic granuloma
Trichosporon infection
Trypanosoma serology positive
Trypanosomiasis
Tuberculid
Tuberculin test false negative
Tuberculin test false positive
Tuberculin test positive
Tuberculoid leprosy[1]
Tuberculoma[1]
Tuberculoma of central nervous system[1]
Tuberculosis[1]
Tuberculosis bladder[1]
Tuberculosis gastrointestinal[1]
Tuberculosis liver[1]
Tuberculosis of central nervous system[1]
Tuberculosis of eye[1]
Tuberculosis of genitourinary system[1]
Tuberculosis of intrathoracic lymph nodes[1]
Tuberculosis of peripheral lymph nodes[1]
Tuberculosis of uterine cervix[1]

Hepatosplenic candidiasis[1]	Tuberculosis ureter[1]
Herpes dermatitis	Tuberculous abscess central nervous system[1]
Herpes gestationis	Tuberculous endometritis[1]
Herpes oesophagitis[1]	Tuberculous laryngitis[1]
	Tuberculous pelvic inflammatory disease[1]
Herpes ophthalmic[1]	Tuberculous pleurisy[1]
Herpes pharyngitis	Tuberculous tenosynovitis[1]
Herpes sepsis[1]	Typhus rickettsia test positive
Herpes simplex	Upper respiratory fungal infection[1]
Herpes simplex bronchitis[1]	Urinary tract candidiasis
Herpes simplex colitis[1]	Urinary tract infection enterococcal
Herpes simplex encephalitis[1]	Urinary tract infection fungal
Herpes simplex gastritis[1]	Urinary tract infection pseudomonal
Herpes simplex hepatitis[1]	Urinary tract infection staphylococcal
Herpes simplex meningitis[1]	Urogenital infection fungal
Herpes simplex meningoencephalitis[1]	Urosepsis
Herpes simplex meningomyelitis[1]	Variant Creutzfeldt-Jakob disease
Herpes simplex necrotising retinopathy[1]	Varicella
	Varicella encephalitis[1]
	Varicella meningitis[1]
Herpes simplex oesophagitis[1]	Varicella post vaccine
Herpes simplex otitis externa[1]	Varicella virus test positive
Herpes simplex pharyngitis	Varicella zoster gastritis[1]
Herpes simplex pneumonia[1]	Varicella zoster oesophagitis[1]
Herpes simplex sepsis[1]	Varicella zoster pneumonia[1]
Herpes simplex test positive	Varicella zoster sepsis[1]

Herpes simplex viraemia[1]	Varicella zoster virus infection
	Vascular access device culture positive
Herpes simplex virus conjunctivitis neonatal	Vibrio test positive
Herpes simplex visceral[1]	Viraemia
Herpes virus infection	Viral myelitis
Herpes zoster	Viral myocarditis
Herpes zoster cutaneous disseminated[1]	Viral oesophagitis
Herpes zoster disseminated[1]	
Herpes zoster infection neurological[1]	Viral pericarditis
Herpes zoster meningitis[1]	Viral sepsis
Herpes zoster meningoencephalitis[1]	Viral test positive
Herpes zoster meningomyelitis[1]	Viral uveitis
Herpes zoster meningoradiculitis[1]	Visceral leishmaniasis[1]
Herpes zoster necrotising retinopathy[1]	Vulvovaginal candidiasis
Herpes zoster oticus[1]	Vulvovaginal human papilloma virus infection
Herpes zoster pharyngitis[1]	Weissella infection[1]
Herpes zoster reactivation[1]	
Histoplasmosis[1]	West Nile viral infection
Histoplasmosis cutaneous[1]	West Nile virus test positive
Histoplasmosis disseminated[1]	Wound infection fungal
Human anaplasmosis	Wound infection pseudomonas
Human ehrlichiosis	Wound infection staphylococcal
Human herpes virus 6 serology positive	Wound sepsis
	WU virus infection
Human herpes virus 8 test positive	Yersinia sepsis

Human herpesvirus 6 encephalitis[1]

Human herpesvirus 6 infection

Yersinia test positive

Zygomatic abscess

[1]Narrow term

8.4.2.6. Central Nervous System Vascular Disorders

The Central nervous system vascular disorders search definition is based on the MedDRA version 27.0 Narrow and Broad Terms from the Haemorrhagic central nervous system vascular conditions SMQ, Ischaemic central nervous system vascular conditions SMQ, and Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic SMQ. The PTs are shown below, with Narrow search terms indicated:

Amaurosis fugax[1]
Amyloid related imaging abnormalities
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
Amyloid related imaging abnormality-oedema/effusion
Basal ganglia haematoma[1]
Basal ganglia haemorrhage[1]
Basal ganglia infarction[1]
Basal ganglia stroke[1]
Basilar artery occlusion[1]
Basilar artery perforation[1]
Basilar artery stenosis[1]
Basilar artery thrombosis[1]
Benedikt's syndrome[1]
Blood brain barrier defect
Brachiocephalic arteriosclerosis[1]
Brachiocephalic artery occlusion[1]
Brachiocephalic artery stenosis[1]
Brain hypoxia[1]
Brain stem embolism[1]
Cerebrovascular disorder[1]
Cerebrovascular insufficiency[1]
Cerebrovascular stenosis[1]
Chronic cerebrospinal venous insufficiency[1]
Claude's syndrome[1]
Congenital cerebrovascular anomaly
Cortical hand stroke[1]
Delayed ischaemic neurological deficit[1]
Dural arteriovenous fistula[1]
Embolic cerebellar infarction[1]
Embolic cerebral infarction[1]
Embolic stroke[1]
Epidural haemorrhage[1]
Extra-axial haemorrhage[1]
Extradural haematoma[1]
Extradural haematoma evacuation[1]
Extraischaemic cerebral haematoma[1]
Foetal cerebrovascular disorder[1]
Foville syndrome[1]
Haemorrhage intracranial[1]

Brain stem haematoma[1]
Brain stem haemorrhage[1]
Brain stem infarction[1]
Brain stem ischaemia[1]
Brain stem microhaemorrhage[1]
Brain stem stroke[1]
Brain stem thrombosis[1]
Brain stent insertion[1]
CADASIL[1]
Capsular warning syndrome[1]
CARASIL syndrome[1]
Carotid aneurysm rupture[1]
Carotid angioplasty[1]
Carotid arterial embolus[1]
Carotid arteriosclerosis[1]
Carotid artery bypass[1]
Carotid artery disease[1]
Carotid artery dolichoectasia
Carotid artery insufficiency[1]
Carotid artery occlusion[1]
Carotid artery perforation[1]
Carotid artery restenosis[1]
Carotid artery stenosis[1]
Carotid artery stent insertion[1]
Haemorrhagic cerebellar infarction[1]
Haemorrhagic cerebral infarction[1]
Haemorrhagic stroke[1]
Haemorrhagic transformation stroke[1]
Hypertensive cerebrovascular disease
Hypoxic-ischaemic encephalopathy[1]
Inner ear infarction[1]
Internal capsule infarction[1]
Intracerebral haematoma evacuation[1]
Intracranial haematoma[1]
Intracranial haemorrhage neonatal[1]
Intracranial tumour haemorrhage[1]
Intraventricular haemorrhage[1]
Intraventricular haemorrhage neonatal[1]
Ischaemic cerebral infarction[1]
Ischaemic stroke[1]
Jugular vein embolism[1]
Lacunar infarction[1]
Lacunar stroke[1]
Lateral medullary syndrome[1]
Medullary compression syndrome
Meningorrhagia[1]
Middle cerebral artery stroke[1]
Migrainous infarction[1]
Millard-Gubler syndrome[1]
Moyamoya disease[1]
Occipital lobe stroke[1]
Parietal lobe stroke[1]
Perinatal stroke[1]
Periventricular haemorrhage neonatal[1]
Pituitary apoplexy[1]

Carotid artery stent removal[1]
Carotid artery thrombosis[1]
Carotid endarterectomy[1]
Carotid revascularisation[1]
Central nervous system haemorrhage[1]
Central nervous system vasculitis[1]
Cerebellar artery occlusion[1]
Cerebellar artery thrombosis[1]
Cerebellar atherosclerosis[1]
Cerebellar embolism[1]
Cerebellar haematoma[1]
Cerebellar haemorrhage[1]
Cerebellar infarction[1]
Cerebellar ischaemia[1]
Cerebellar microhaemorrhage[1]
Cerebellar stroke[1]
Cerebral amyloid angiopathy
Cerebral aneurysm perforation[1]
Cerebral aneurysm ruptured syphilitic[1]
Cerebral angioplasty[1]
Cerebral arteriosclerosis[1]
Cerebral arteriovenous malformation haemorrhagic[1]
Cerebral arteritis[1]
Cerebral artery embolism[1]
Cerebral artery occlusion[1]
Cerebral artery perforation[1]
Cerebral artery restenosis[1]
Cerebral artery stenosis[1]
Cerebral artery stent insertion[1]
Cerebral artery thrombosis[1]
Cerebral bypass surgery[1]
Pituitary haemorrhage[1]
Post cardiac arrest syndrome[1]
Post procedural stroke[1]
Precerebral arteriosclerosis[1]
Precerebral artery embolism[1]
Precerebral artery occlusion[1]
Precerebral artery thrombosis[1]
Primary familial brain calcification
Pseudo-occlusion of internal carotid artery[1]
Putamen haemorrhage[1]
Retinal artery occlusion[1]
Reversible cerebral vasoconstriction syndrome[1]
Reversible ischaemic neurological deficit[1]
Ruptured cerebral aneurysm[1]
Sigmoid sinus thrombosis[1]
Sneddon's syndrome
Spinal artery embolism[1]
Spinal artery thrombosis[1]
Spinal cord haematoma[1]
Spinal cord haemorrhage[1]
Spinal cord hypoxia[1]
Spinal cord infarction[1]
Spinal cord ischaemia[1]
Spinal epidural haematoma[1]
Spinal epidural haemorrhage[1]
Spinal stroke[1]
Spinal subarachnoid haemorrhage[1]
Spinal subdural haematoma[1]
Spinal subdural haemorrhage[1]
Spinal vascular disorder
Spinal vessel congenital anomaly
Stroke in evolution[1]
Subarachnoid haematoma[1]

Cerebral capillary telangiectasia[1]	Subarachnoid haemorrhage[1]
Cerebral circulatory failure[1]	Subarachnoid haemorrhage neonatal[1]
Cerebral congestion[1]	Subclavian steal syndrome[1]
	Subcortical stroke[1]
Cerebral cyst haemorrhage[1]	Subdural haematoma[1]
Cerebral gas embolism[1]	Subdural haematoma evacuation[1]
Cerebral haematoma[1]	Subdural haemorrhage[1]
Cerebral haemorrhage[1]	Subdural haemorrhage neonatal[1]
Cerebral haemorrhage foetal[1]	Superior sagittal sinus thrombosis[1]
Cerebral haemorrhage neonatal[1]	Susac's syndrome
	Temporal artery stenosis[1]
Cerebral hypoperfusion[1]	Thalamic infarction[1]
	Thalamic stroke[1]
Cerebral infarction[1]	Thalamus haemorrhage[1]
Cerebral infarction foetal[1]	Thrombotic cerebral infarction[1]
Cerebral ischaemia[1]	Thrombotic stroke[1]
Cerebral microangiopathy	Transient ischaemic attack[1]
Cerebral microembolism[1]	Transverse sinus thrombosis[1]
Cerebral microhaemorrhage[1]	Vascular encephalopathy[1]
Cerebral microinfarction[1]	Vascular stent occlusion[1]
Cerebral revascularisation[1]	Vascular stent stenosis[1]
Cerebral septic infarct[1]	Vertebral artery arteriosclerosis[1]
Cerebral small vessel ischaemic disease[1]	Vertebral artery occlusion[1]
Cerebral thrombosis[1]	Vertebral artery perforation[1]
Cerebral vascular occlusion[1]	Vertebral artery stenosis[1]
Cerebral vasoconstriction[1]	Vertebral artery thrombosis[1]
Cerebral venous sinus thrombosis[1]	Vertebrobasilar dolichoectasia
	Vertebrobasilar infarction[1]
Cerebral venous thrombosis[1]	Vertebrobasilar insufficiency[1]
Cerebrovascular accident[1]	Vertebrobasilar stroke[1]
Cerebrovascular arteriovenous malformation	Weber's syndrome[1]

[1]Narrow term.

8.4.2.7. Embolic and Thrombotic Events

The Embolic and thrombotic events search definition is based on the MedDRA version 27.0 Embolic and thrombotic events, venous SMQ. The PTs are listed below, and all will be considered Narrow search terms:

Aseptic cavernous sinus thrombosis
Axillary vein thrombosis
Brachiocephalic vein occlusion

Brachiocephalic vein thrombosis
Budd-Chiari syndrome
Catheterisation venous
Cavernous sinus thrombosis
Central venous catheterisation
Cerebral venous sinus thrombosis
Cerebral venous thrombosis
Compression garment application
Deep vein thrombosis
Deep vein thrombosis postoperative
Embolism venous

Hepatic vein embolism
Hepatic vein occlusion

Hepatic vein thrombosis
Homans' sign positive
Iliac vein occlusion
Inferior vena cava syndrome
Inferior vena caval occlusion
Jugular vein embolism
Jugular vein occlusion
Jugular vein thrombosis
Mahler sign
May-Thurner syndrome
Mesenteric vein embolism
Mesenteric vein thrombosis
Mesenteric venous occlusion

Obstetrical pulmonary embolism
Obstructive shock
Ophthalmic vein thrombosis
Ovarian vein thrombosis
Pulmonary embolism
Pulmonary infarction
Pulmonary microemboli
Pulmonary oil microembolism
Pulmonary thrombosis
Pulmonary vein occlusion
Pulmonary veno-occlusive disease
Pulmonary venous thrombosis
Renal vein embolism
Renal vein occlusion
Renal vein thrombosis
Retinal vein occlusion
Retinal vein thrombosis
Septic pulmonary embolism
SI QIII TIII pattern
Sigmoid sinus thrombosis
Spermatic vein thrombosis
Splenic vein occlusion
Splenic vein thrombosis
Subclavian vein embolism
Subclavian vein occlusion
Subclavian vein thrombosis
Superior sagittal sinus thrombosis
Superior vena cava occlusion
Superior vena cava syndrome
Thrombophlebitis
Thrombophlebitis migrans
Thrombophlebitis neonatal

Thrombosed varicose vein

Thrombosis corpora cavernosa
Transverse sinus thrombosis
Vascular graft
Vena cava embolism
Vena cava filter insertion
Vena cava filter removal
Vena cava thrombosis

Paget-Schroetter syndrome	Venogram abnormal
Pelvic venous thrombosis	Venoocclusive disease
Penile vein thrombosis	Venoocclusive liver disease
Peripheral vein occlusion	Venous angioplasty
Peripheral vein thrombosis	
Peripheral vein thrombus extension	Venous occlusion
Phlebectomy	Venous operation
Portal vein cavernous transformation	Venous recanalisation
Portal vein embolism	Venous repair
Portal vein occlusion	Venous stent insertion
Portal vein thrombosis	Venous thrombosis
Portosplenomesenteric venous thrombosis	Venous thrombosis in pregnancy
Post procedural pulmonary embolism	Venous thrombosis limb
Post thrombotic syndrome	Venous thrombosis neonatal
Postoperative thrombosis	Visceral venous thrombosis
Postpartum venous thrombosis	

8.4.2.8. Cardiac Rhythm Disturbances

The Cardiac rhythm disturbances search definition is based on the MedDRA version 27.0 Narrow and Broad Terms from the Arrhythmia related investigations, signs and symptoms SMQ. The PTs are shown below, with Narrow search terms indicated:

Chronotropic incompetence[1]	Electrocardiogram ambulatory abnormal
Early repolarisation syndrome[1]	
Electrocardiogram repolarisation abnormality[1]	Electrocardiogram change
Electrocardiogram RR interval abnormal[1]	
Electrocardiogram RR interval prolonged[1]	Heart rate abnormal
Electrocardiogram RR interval shortened[1]	
Electrocardiogram U wave inversion[1]	Heart rate decreased
Electrocardiogram U wave present[1]	Heart rate increased
Electrocardiogram U-wave abnormality[1]	Loss of consciousness
Sudden cardiac death[1]	Palpitations
Bezold-Jarisch reflex	Rebound tachycardia
Bradycardia	Respiratory sinus arrhythmia magnitude abnormal
Cardiac arrest	Respiratory sinus arrhythmia magnitude decreased
Cardiac death	Respiratory sinus arrhythmia magnitude

	increased
Cardiac telemetry abnormal	Sudden death
Cardio-respiratory arrest	Syncope
Central bradycardia	Tachycardia
Cerebrocardiac syndrome	
Electrocardiogram abnormal	Tachycardia paroxysmal

[1]Narrow term

8.4.2.9. Upper Respiratory Tract Infections

The Upper respiratory tract infections search definition based on the following selected MedDRA version 27.0 PTs:

Acute sinusitis	Sinusitis
Upper respiratory tract infection	Viral upper respiratory tract infection

8.4.2.10. Diarrhea

The Diarrhea search definition is based on the MedDRA version 27.0 PT of Diarrhoea.

Plan Version History

Version	Effective Date	Changes	Author / Modified by
1.0	17-Feb-2023	NA	Steven Chang
2.0	03-Jun-2024	See summary below	Eve Zeng
3.0	28-Oct-2024	See summary below	Steven Chang

Change History Summary

Version	Modifications
1.0	Initial Version
2.0	PFS-6 was redefined as a survival probability for consistency with the Kaplan-Meier methodology which was intended to be used to estimate this endpoint.
2.0	Definitions and analysis methods were added for PFS and OS.
2.0	Progression-free survival on continued nirogacestat treatment and PFS2 were added due to protocol amendment.
2.0	Miscellaneous formatting and typographical changes.
2.0	Statement was added for why the planned interim assessment using Bayesian approach as mentioned in the protocol was not performed.
2.0	Analysis of safety topics of special interest identified using standardized MedDRA queries (SMQ) or customized MedDRA queries was added.
3.0	Section 5.6.2 - Added a summary table for serious TEAEs by maximum severity (Grade)
3.0	Section 5.6.6 - Rows for the worst post-baseline change from baseline added to the ECG summary table.
3.0	Section 5.6.7 - Rows for the worst post-baseline change from baseline added to the vital signs summary table.
3.0	Section 8.4.1.4 Electrolyte disorder PTs were revised. Added new electrolyte disorder analyses (summary table and shift table).

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The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

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