Statistical Analysis Plan

Olema Pharmaceuticals, Inc.

OP-1250-001

A Phase I Dose Escalation and Dose Expansion and Phase II Monotherapy Open-label, First-in-Human, Multicenter Study of OP-1250 in Adult Subjects with Advanced and/or Metastatic Hormone Receptor (HR)-Positive, HER2-Negative Breast Cancer

Protocol Amendment 7: 16 April 2024

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LIST OF ABBREVIATIONS

Abbreviation	Full Notation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BC	Breast cancer
BMI	Body mass index
CBR	Clinical benefit rate
CI	Confidence interval
C_{max}	Maximum concentration
C_{min}	Mininum concentration
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	[redacted]
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EOT	End of Treatment
ESR1	Estrogen Receptor 1
FAS	Full analysis set
HR	Hormone receptor
[redacted]	[redacted]
ICH	International Council for Harmonisation
IRC	Independent Review Committee
[redacted]	[redacted]
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute

[redacted]

NE	Not evaluable
ORR	Overall response rate
PD	Progressive disease
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PP	Per protocol
PR	Partial response
PT	Preferred term
QC	Quality control
QD	Quaque die (daily)
QTc	Corrected QT interval
QTcF	Corrected QT interval according to Fridericia's formula
[redacted]	[redacted]
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
t½	Half-life
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings, and figures
T_{max}	Time to maximum concentration
[redacted]	[redacted]
ULN	Upper limit of normal range
WHO	World Health Organization

[redacted]

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Olema Pharmaceuticals, Inc. protocol OP-1250-001 (A Phase I Dose Escalation and Dose Expansion and Phase II Monotherapy Open-label, First-in-Human, Multicenter Study of OP-1250 in Adult Subjects with Advanced and/or Metastatic Hormone Receptor (HR)-Positive, HER2-Negative Breast Cancer (BC)). The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

Phase I (Dose Escalation Part A and Expansion Part B)

2.1 Primary Objectives

- To identify the dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of OP-1250 (Part A).
- To confirm the RP2D of OP-1250 (Part B).
- To assess the safety and tolerability of OP-1250 (Parts A and B).
- To assess the pharmacokinetics (PK) of OP-1250 (Parts A and B).

2.2 Secondary Objectives (Parts A and B)

- To estimate the overall response rate (ORR) defined as the complete response (CR) + partial response (PR) rate of OP-1250.
- To estimate the clinical benefit rate (CBR) (CR+PR + stable disease (SD) ≥ 24 weeks) of OP-1250.

[redacted]

[redacted]

Phase II

2.4 Primary Objectives

- To estimate the ORR of OP-1250 in subjects with HR+/HER2- metastatic or locally advanced BC-with no evidence of central nervous system (CNS) metastases who have progressed following at least 1 hormonal therapy regimen in the metastatic or locally advanced setting.
- To assess the safety and tolerability of OP-1250.
- To assess the plasma PK profile of OP-1250.

2.5 Secondary Objectives

- To estimate the CBR of OP-1250 in subjects with HR+/HER2- metastatic or locally advanced BC with no evidence of CNS metastases who have progressed after receiving at least 1 hormonal treatment regimen in the metastatic or locally advanced setting.

[redacted]

3. STUDY ENDPOINTS

The study endpoints of each of the 2 phases of the study are:

Phase I (Dose Escalation and Expansion)
Primary Endpoints:

- Incidence and nature of DLTs as defined in the protocol.
- MTD and/or RP2D of OP-1250 when used as a single agent.
- Incidence, nature, and severity of treatment-emergent Adverse Events (TEAEs) and serious adverse events (SAEs) according to NCI-CTCAE version 5.0.
- Plasma levels of OP-1250 at pre-defined intervals to establish PK parameters (includes maximum concentration (Cmax), minimum concentration (Cmin), time to maximum concentration (Tmax), area under the curve (AUC), half-life ($t_{1/2}$), and OP-1250 trough concentration at steady state).

Secondary Endpoints:

- ORR by evaluation of tumor response assessments using RECIST 1.1 in subjects with measurable disease.
- CBR as defined by percent of subjects with CR + PR + SD ≥ 24 weeks, by evaluation of tumor response assessments using RECIST 1.1.
- [redacted]

[redacted]

[redacted]

Phase II

Primary Endpoints:

- ORR by evaluation of tumor response assessments using RECIST 1.1 in subjects without evidence of CNS metastases who have measurable disease.
- Incidence, nature, and severity of TEAEs and SAEs according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.
- Plasma levels of OP-1250 at pre-defined intervals to establish PK parameters (includes Cmax, Cmin, Tmax, AUC, t½, and OP-1250 trough concentration at steady state). The results of those analyses will be reported separately in PK report.

Secondary Endpoints:

- CBR as defined by percent of subjects with a CR + PR + SD for ≥ 24 weeks, by evaluation of tumor response assessments using RECIST 1.1 in subjects without evidence of CNS metastases.

[redacted]

4. STUDY DESIGN AND PLAN

This is a Phase I dose escalation, dose expansion and Phase II open-label, first-in-human study to determine the DLT, MTD, and/or RP2D, to characterize the safety and PK profile, and to estimate the preliminary anti-tumor activity of OP-1250 as a single agent in adult subjects with Hormone Receptor positive (HR+)/Human epidermal growth factor receptor 2 negative (HER2-) metastatic or locally advanced BC. Treatment and study subject evaluation will be performed in 28-day cycles. In the absence of unacceptable OP-1250 treatment-related toxicity or disease progression, subjects may receive OP-1250 treatment for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor.

Radiographic and/or physical assessments of the malignancy will be made at screening/baseline (within 28 days before the first study drug administration) and after every 2 cycles of treatment. Subjects who have been determined to have obtained a clinical benefit from OP-1250 may decrease the frequency of radiographic and physical assessments of malignancy to every 3 months after the Cycle 8 radiographic assessment. Tumor response will be assessed using RECIST 1.1. [redacted]

This study comprises 2 Phases: Phase I (Part A and Part B), and Phase II.

Phase I

The rolling 6 dose escalation rules will be employed, considering DLTs observed in Cycle 1. Cohorts of 3 to 6 subjects will be treated at each dose level.

At the end of Phase I, Part A, a comprehensive review of safety, tolerability, and PK data will be performed to assess whether one OP-1250 dose can be identified as the Recommended Phase 2 Dose (RP2D). If this comprehensive review is equivocal on two OP-1250 doses as the possible RP2D, then these two doses will be investigated in Phase I, Part B.

Part B (Dose Expansion)

If one dose is clearly identified during dose escalation in Phase I, Part A as the RP2D, then approximately 30 additional subjects will be enrolled at this dose. If two OP-1250 doses are advanced from Phase I, Part A, then each dose will enroll approximately 30 additional subjects, for a total of approximately 60 subjects.

At the end of Phase I, Part B, a comprehensive review of safety, tolerability, PK and preliminary antitumor activity data will be performed. If only one dose was advanced from Phase I, Part A, i.e., a RP2D was already identified, then the purpose of this comprehensive review will be to assess a preliminary risk:benefit ratio to enable safe enrollment of additional subjects in the Phase II. If two doses

[redacted]

are advanced from Phase I, Part A, then the purpose of this comprehensive review will be 2-fold: first, to select the RP2D, and second, to assess a preliminary risk:benefit ratio of the RP2D to enable safe enrollment of additional subjects in the Phase II, Expansion part of the study.

Phase II

This portion of the study further explores the clinical activity, safety and PK of OP-1250 monotherapy at the RP2D and estimates the preliminary anti-tumor activity. Up to 80 evaluable subjects will be enrolled over 3 cohorts in Phase II as follows:

- Cohort A will enroll approximately 50 subjects with measurable disease without evidence of CNS metastases.
- Cohort B will enroll approximately 15 subjects with non-measurable (evaluable) disease without evidence of CNS metastases.
- Cohort C will enroll up to 15 subjects with CNS metastases.

Additional subjects may be enrolled to allow for subject drop-out. To allow for subject replacement, up to 88 subjects may be enrolled in the Phase II portion of the study.

[redacted]

5. DETERMINATION OF SAMPLE SIZE

5.1 Phase I (Part A Dose Escalation)

For Phase I, Part A, cohorts of 3 to 6 subjects will be enrolled in each OP-1250 dose cohort based on a rolling 6 dose escalation scheme. Each subject will participate in only 1 dose cohort. The total number of subjects to be enrolled in the dose escalation phase of the study is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD. Approximately up to 42 subjects will participate in Phase 1, Part A dose escalation.

5.2 Phase I (Part B Dose Expansion)

Up to approximately 60 subjects with measurable disease will participate in Phase I, Part B dose expansion. If 1 dose is clearly identified during dose escalation in Phase I Part A as the RP2D, then 30 subjects will be enrolled at this dose. If 2 OP-1250 doses are advanced from Phase I, Part A, then each dose will enroll approximately 30 subjects for a total of up to approximately 60 subjects.

A sample size of 30 subjects per dose group will provide an estimation precision of ±19% per dose group for any binary event rate assessing safety, tolerability, anti-tumor activity (e.g., overall response, clinical

benefit) or exposure/kinetics. This level of precision is regarded as clinically sufficient in the comprehensive review of safety, tolerability, PK and preliminary anti-tumor activity data to gate enrollment into the Phase II part of the study.

5.3 Phase II

Approximately a total of 80 additional subjects will be enrolled in the expansion phase: 50 subjects in Cohort A, 15 in Cohort B, and 15 in Cohort C. Subjects not evaluable may be replaced.

For the statistical analyses of ORR, data from the 50 subjects in Cohort A who were dosed at the RP2D will be included. A sample size of 50 subjects will provide an estimation precision of ±15% for any binary event assessing safety (e.g., any SAE's) or anti-tumor activity (e.g., overall response, clinical benefit). This level of precision is regarded as clinically sufficient in the preliminary estimation of the risk:benefit profile to plan future clinical trials for OP-1250's clinical development plan.

Subjects without measurable disease are being enrolled in the Phase II study (Cohort B) in order to mimic the general population of ER+ breast cancer subjects, many of which have bone only disease. Subjects without measurable disease in the Phase II are limited to a total of 15 subjects and will not be included in the determination of ORR; however, they will be included in safety, secondary, and exploratory analyses where appropriate [redacted]

[redacted]

6. GENERAL ANALYSIS CONSIDERATIONS

6.1 Statistical Analysis Cohorts

Statistical analysis will be conducted in the cohorts below.

1. Dose Escalation subjects: All endpoints [redacted] will be summarized by dose groups.
2. Subjects treated at 60 mg or 120 mg pooled from dose escalation, dose expansion and phase II (without cohort C): The study subjects and demographic, pharmacodynamic endpoints, and efficacy endpoints will be analyzed by dose groups.

[redacted]

4. All subjects: All safety related endpoints will be summarized based on the safety analysis set by dose groups, [redacted] and overall.

For summary by dose groups, the dose groups will be based on the first doses the subjects received.

[redacted]

6.2 Statistical Analysis Methods

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs.

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum).

Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories.

Baseline is defined as the last non-missing assessment prior to the first dose of OP-1250. If an assessment is on the same date as first dose of OP-1250 and time of assessment is not recorded, the assessment will be considered to have occurred prior to the first dose.

All summary tables will be presented with separate columns for each OP-1250 dose.
Individual subject data obtained from the eCRFs, external vendors, and any derived data may be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock.

All analyses, tabulations, and graphical presentations will be performed using SAS® software version 9.4 or higher.

7. NOTATION OF VISITS

Table 1: Visit Terminology

Visit	Notation Used
Screening	Screening/Baseline[a]
Baseline, Cycle 1 Day 1	Baseline
Cycle 1 Day 8	C1D8
Cycle 1 Day 15	C1D15
Cycle 2 Day 1	C2D1
Cycle 2 Day 15	C2D15
Cycle 3 Day 1	C3D1
Cycle 3 Day 15	C3D15
Cycle 4 Day 1	C4D1
Cycle 4 Day 15	C4D15
Cycle X Day 1[b]	CXD1
Treatment Termination	Treatment Termination

[a] Assessments from screening visit may be used for baseline if they are last assessment before first dose of study drug.
[b] Visits will continue on Day 1 of each cycle until subject terminates treatment.

8. ANALYSIS SETS

8.1 Enrolled Analysis Set

The enrolled analysis set (ENR) includes all subjects who enrolled into the study after signing an informed consent form and satisfying inclusion/exclusion criteria.

8.2 Safety Analysis Set

The safety analysis set (SAF) will include all subjects who received at least 1 full or partial dose of OP-1250. Subjects will be analyzed according to the OP-1250 doses they actually received as a first dose. The safety analysis set will be used for all safety analyses except for the analyses of DLTs.

8.3 DLT Evaluable Analysis Set

The DLT evaluable analysis set (DLTAS) includes all subjects in the dose escalation portion of the study who either received at least 75% of the OP-1250 planned doses or experienced a DLT during Cycle 1. Subjects who do not receive the minimum dosing requirement for a reason other than DLT will be regarded as non-evaluable and may be replaced.

8.4 Full Analysis Set

The full analysis set (FAS) includes all subjects who received at least 1 dose of OP-1250 and have at least 1 post-baseline tumor assessment.

8.5 Efficacy Analysis Set

The efficacy analysis set (EFS) will include all subjects who received at least 1 cycle of OP-1250 and have at least 1 post-baseline tumor assessment.

8.6 Clinical Benefit Rate (CBR) Analysis Set

The CBR analysis set (CBRAS) will include subjects in EFS, who started their first dose 24 weeks before data cut off. Subjects who are on treatment for less than 24 weeks, without radiographic progression per RECIST 1.1 will be excluded.

8.7 Pharmacokinetic Analysis Set

The PK analysis set consists of all subjects who received at least 1 full or partial dose of OP-1250 and have adequate PK samples for PK parameter characterization.

9. STUDY SUBJECTS AND DEMOGRAPHICS

9.1 Subject Disposition

Subject disposition summary will include: the number of subjects in each analysis set, the number of subjects discontinued the study treatment, the primary reason for study treatment discontinuation, the number of subjects completed the study, the number of subjects discontinued the study early, and the primary reason for study discontinuation.

9.2 Protocol Deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being and will be identified before database lock. Important protocol deviations may include, but are not limited to:

- Enrolled subjects who did not satisfy selected inclusion and exclusion criteria.
- Enrolled subjects who developed withdrawal criteria during the study but were not withdrawn.
- Subjects who received the incorrect dose.
- Subjects who received a prohibited medication.

Important protocol deviations will be summarized by deviation category.

9.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics and cancer history will be summarized for the safety analysis set.
Demographic variables include age, age group, sex, ethnicity, and race. Age will be calculated in years relative to the informed consent date.

Other baseline characteristics include height, weight, body mass index (BMI), Eastern Cooperative Oncology Group Performance Status (ECOG PS), menopausal status (for females)[redacted]

The summary of cancer history will include but not limited to the following characteristics:

- Time from initial metastatic or recurrent BC diagnosis to first dose date
- Brain metastases at initial metastatic or recurrent BC diagnosis (yes/no)
- Overall grade at time of initial metastatic or recurrent BC diagnosis
- Histology at time of initial metastatic or recurrent BC diagnosis
- Estrogen receptor status at time of initial metastatic or recurrent BC diagnosis
- Progesterone receptor status at time of initial metastatic or recurrent BC diagnosis
- HER2 status at time of initial metastatic or recurrent BC diagnosis
- Surgery for metastatic or recurrent BC (yes/no, type)
- Radiotherapy for metastatic or recurrent BC (yes/no)
- Sites of disease at study entry

[redacted]

- Overall grade at study entry
- Estrogen receptor status at study entry
- Progesterone receptor status at study entry
- HER2 status at study entry
- Visceral disease

The prior systemic treatment for metastatic or recurrent breast cancer will include the followings:

- Number of systemic treatment regimens for metastatic or recurrent BC
- Number of systemic hormonal treatment regimens for metastatic or recurrent BC
- Types of therapies

9.4 Medical history

The verbatim term of the medical history condition/event will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A summary will be presented by system organ class (SOC) and preferred term (PT).

9.5 Prior and Concomitant Medications

Prior and concomitant medication will be summarized for the safety analysis set.

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Preferred Names using World Health Organization (WHO) Drug Global Dictionary WHODDE B3 March 1, 2020.

Concomitant medications are those started after the initial dose of OP-1250 through last dose + 30 days or medications started prior to initial dose of OP-1250 and continued during the treatment period. Prior medications are those that started prior to initial dose of study drug. Note that medications can be classified as both prior and concomitant.
Concomitant medications will be summarized by WHO ATC class and preferred name. This summary will present the numbers and percentages of subjects using each medication. Subjects may have more than 1 medications per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level.

10. EFFICACY ANALYSES

Efficacy analyses for ORR [redacted] by investigator assessment will be conducted using EFS with measurable disease at baseline (without cohort C). CBR by investigator assessment will be summarized using CBR analysis set. [redacted]

[redacted]

[redacted]

[redacted]

10.1 Efficacy Endpoints

ORR

ORR is the primary efficacy endpoint in phase II (without cohort C) and secondary endpoint in phase I. Objective response will be determined using RECIST version 1.1. The overall tumor response at each time point will be recorded. A subject's best overall response will be derived as the best response over all time points, where responses from best to worst are CR, PR, SD, progressive disease (PD), and not evaluable (NE). Time point responses after the first assessment of PD will not be used in the derivation of confirmed best objective response. A confirmed response requires a CR or PR to be confirmed at a subsequent tumor assessment at least 4 weeks (28 days) from the initial assessment of CR or PR, and a confirmed response of SD requires the interval from first dose date to SD to be at least 6 weeks (42 days). To determine the best overall confirmed response in the presence of at least one time point response of CR or PR, the best response for each pair of assessments will be derived based on Table 2. The best overall confirmed response will then be the best over all of the pair best responses.

Table 2: Derivation of Best Overall Response when confirmation of CR and PR required

Overall response for 1st time point	Overall response for subsequent time point	Best overall response for pair of assessments
CR	CR	CR if time requirement is met, otherwise NE
CR	PR	SD or PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR

[redacted]

PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable.
[a] : If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

The confirmed ORR is defined as the proportion of subjects with a best overall response of confirmed CR or PR in EFS with measurable disease at baseline.

The secondary efficacy endpoints for Phase II are:

CBR

CBR is defined as the proportion of subjects with a confirmed CR, PR, or SD and who had been on treatment for ≥ 24 weeks. Subjects who had disease progression per RECIST 1.1 7 days before Cycle 7 day 1 will not be considered as clinical benefit. Duration of treatment is defined as time from the first dose date of study treatment to end of treatment date for subjects discontinued treatment or to data cutoff date for ongoing subjects.

CBR will be summarized based on CBR Analysis Set (without cohort C) defined in 8.6.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

10.2 Methods Of Efficacy Analysis

The ORR and CBR will be summarized with frequencies and percentages. The exact 95% confidence interval (CI) via the Clopper-Pearson method will be constructed for the ORR and CBR.

A waterfall plot will plot the best percentage change from baseline (or maximum decrease from baseline) in sum of the longest diameters (short axis for measurable lymph node) of target lesions for each subject, plotted in order from greatest percentage change to smallest. The OP-1250 dose will be presented in the plot with different colors. Changes in tumor burden by time point may be summarized.

A swimmer's plot will display overall tumor response over time and include prior therapies in the advanced setting. Patients will be grouped by OP-1250 dose.

[redacted]

10.3 Baseline Values

For efficacy purposes, baseline is defined as the last disease assessment conducted on or before the date of first dose of study drug.

[redacted]

10.4 Adjustments for Covariates

No adjustments for covariates are planned.

10.5 Handling of Dropouts or Missing Data

No imputation will be done for missing disease assessments.

10.6 Interim Analysis and Data Monitoring

No formal interim analysis will be conducted.

[redacted]

10.8 Multiple Comparison/Multiplicity

No adjustments for multiplicity will be made in this study.

10.9 Multicenter Studies

Differences in response by center will not be prospectively analyzed for this preliminary evaluation of efficacy of OP-1250.

[redacted]

[redacted]

12. PHARMACOKINETIC ANALYSES

The PK analyses will be described in a separate PK analysis plan.

13. SAFETY ANALYSES

Dose-limiting toxicities will be summarized in the DLT evaluable analysis set. All other safety analyses will be based on the safety analysis set.

13.1 Dose-Limiting Toxicity

Subjects must receive at least 75% (21 days) of planned OP-1250 dose in Cycle 1 in order to be evaluated for determination of DLTs. Subjects receiving less than 75% of the planned dose for reasons other than experiencing a DLT will be replaced in the dose escalation part of the study. Subjects who receive less than 75% of the study drug due to occurrence of a DLT are considered DLT evaluable and will not be replaced. (Subjects receiving less than 75% of the planned dose in Cycle 1 for reasons other than experiencing a DLT will be evaluated in the overall safety analysis but not for the purpose of dose escalation).

A DLT is defined as the occurrence of any of the following treatment-emergent adverse events (TEAE) graded using NCI-CTCAE v5.0 during Cycle 1 except those that are clearly and incontrovertibly due to disease progression or extraneous causes:

- Any death not clearly due to the underlying disease or extraneous causes
- Grade ≥ 3 non-hematologic toxicity (unless otherwise noted below)
- Grade ≥ 3 nausea and/or vomiting and/or Grade 3 diarrhea not resolving within 72 hours with optimal treatment
- Grade 3 neutropenia accompanied with fever and/or infection
- Grade 3 thrombocytopenia associated with bleeding
- Grade ≥ 4 hematologic toxicity
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x the upper limit of normal (ULN) and a total bilirubin > 2x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase) and no other reason for the increase in transaminases and total bilirubin
- AST or ALT > 8x ULN or AST or ALT >5x ULN for ≥ 14 days
- AST or ALT > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Grade ≥ 3 blurred vision or retinopathy
- Grade ≥ 3 fatigue that does NOT resolve to grade ≤ 1 within 7 days
- Grade ≥ 2 TEAEs that result in omission of treatment for ≥ 7 days during Cycle 1 or delay of Cycle 2 for ≥ 7 days

Multiple concurrent AEs in a single subject leading to DLT will be considered a single DLT.

The MTD is defined as the highest feasible dose tested in which fewer than 33% of subjects experienced a DLT attributable to the study drug, when at least 6 subjects were treated at that dose and were assessable for toxicity.

13.2 Adverse Events

Adverse events will be collected from the time of signing of the informed consent until 30 days following the last dose of study treatment or until resolution/stabilization of any ongoing drug related AEs.

All AE summaries will be restricted to TEAEs, which are defined as those AEs with onset or worsening after the first administration of study drug till the 30 days following the last dose of study drug or any study drug related AEs. Appendix A contains rules for how partial dates will be handled. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such. Verbatim terms in the eCRFs will be mapped to (PT and SOC using MedDRA. Adverse events will be assigned a severity grade per NCI-CTCAE version 5.0. For summaries of maximum CTCAE grade, at each level of subject summarization, a subject is classified according to the highest grade if the subject reported 1 or more events. For summaries of TEAEs that are related to OP-1250, a TEAE is considered related to OP-1250 if it is reported by the Investigator as related, probably related, or possibly related.

AE summaries will be presented by OP-1250 dose using SAF set. Summaries that are displayed by SOC and PTs will be ordered by descending frequency of the total column by SOC and by descending frequency of PT within SOC. Summaries of the following types will be presented:

- Overall summary of TEAEs that contain an overview of each item below.
- Subject incidence of DLTs and total number of unique DLTs by MedDRA SOC and PT in the DLT evaluable analysis set.
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA SOC and PT.
- Subject incidence of grade 3 or greater TEAEs and total number of unique grade 3 or greater TEAEs by MedDRA SOC and PT.
- Subject incidence of OP-1250-related TEAEs and total number of unique OP-1250-related TEAEs by MedDRA SOC and PT.
- Subject incidence of grade 3 or greater OP-1250-related TEAEs and total number of unique grade 3 or greater OP-1250-related TEAEs by MedDRA SOC and PT.
- Subject incidence of TEAEs by MedDRA SOC, PT, and maximum CTCAE grade.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA SOC and PT.
- Subject incidence of OP-1250-related serious TEAEs and total number of unique OP-1250-related serious TEAEs by MedDRA SOC and PT.
- Subject incidence of TEAEs leading to death as an outcome by MedDRA SOC and PT.
- Subject incidence of TEAEs leading to OP-1250 treatment discontinuation, dose reduction and drug withheld by MedDRA SOC and PT.

If any adverse events of special interest (AESI) are identified throughout the study, subject incidence of each AESI and the total number of unique AESIs will be presented.

Separate listings of all SAEs, all AEs leading to OP-1250 treatment discontinuation, and all AEs resulting in death will be provided. A listing of all deaths will also be presented.

13.3 Extent of Exposure

The analysis will be conducted using SAF set.

Study drug exposure will be summarized using the total number of doses received, total number of cycles, duration of study treatment, relative dose intensity, number of dose interruption, and number of dose reduction. Duration of treatment in weeks is defined as the (last dose date - the first dose date + 1)/7. Relative dose intensity will be calculated as the total amount of dose received divided by (the duration on treatment (in days) × assigned dose). The number of subjects with dose interruption, dose reduction and the reason of dose interruption, dose reduction, the number of dose interruptions and dose reductions will be summarized by frequencies and percentages.

13.4 Clinical Laboratory Evaluation

Local laboratories will be used for laboratory safety evaluations in this study. Laboratory parameters (serum chemistry and hematology) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized.

The following laboratory parameters will be graded according to CTCAE v5.0: hemoglobin, platelets, neutrophils, alkaline phosphatase, AST, ALT, creatinine, glucose, lactate dehydrogenase (LDH), potassium, sodium, and total bilirubin. Shift tables assessing changes from baseline to the maximum post-baseline CTCAE grade will also be presented.

The incidence of CTCAE grade ≥ 3 serum chemistry and hematology results will also be summarized for the parameters listed above.

13.5 Vital Signs

Vital signs (blood pressure, heart rate, respiration, temperature, and weight) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized.

13.6 Electrocardiogram

The Corrected QT interval according to Fridericia's formula (QTcF) and heart rate (HR) from electrocardiogram (ECG) data analysis will be conducted based on methodology recommended in the ICH E14 guideline[2] (International Council for Harmonisation, 2005).

Descriptive statistics (for the average of the triplicate measurements) at baseline and the maximum of post-baseline as well as changes from baseline will be summarized for QTcF and HR.

13.7 ECOG Performance Status

Eastern cooperative oncology group (ECOG) performance status (PS) scores will be summarized by the shift from baseline to each post-baseline visit.

14. REFERENCES

[redacted]

2. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Guidance for Industry. ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2012 [cited 2021 Mar 05]. Available from: https://www.fda.gov/media/71372/download.

3. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Guidance for Industry. ICH E9 Statistical principles for clinical trials. September 1998 [cited 2021 Mar 05]. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

15. APPENDICES

APPENDIX A: IMPUTATION RULES FOR PARTIAL AND MISSING DATES

Missing or Incomplete Dates (ie, AEs and Concomitant Medications)

The most conservative approach will be systematically considered. If the AE onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (ie, considered a TEAE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant treatment.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (eg, UN-UNK-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and the stop date is either after the first dose of study drug or completely missing, then the start date will be estimated to be equal to the date of the first dose of study drug. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and nonconcomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing, and January 1 will be used if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to be the last day of the month (eg, UN-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (eg, UN-UNK-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first dose of study drug, and the stop date will be imputed using the last known date on the study.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days** – A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the formulas noted below:

  duration in days = date2 – date1 + 1
- **Months –** is calculated as duration in days/30.4375.
- **Years –** is calculated as duration in days/365.25.
- **Body Mass Index (BMI)** – BMI is calculated using height (cm) and weight (kg) using the following formula:
  BMI (kg/m^2) = weight (kg)/[[height (cm)/100]^2].
- **Change from baseline** – Change from baseline will be calculated as:
  Change = post-baseline value – baseline value.