CLINICAL STUDY PROTOCOL

Study Title: 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 Number:	OP-1250-001
Investigational Product:	OP-1250
US IND Number:	147429
Indication:	Hormone Receptor (HR)-positive, HER2-negative metastatic or locally advanced breast cancer
Sponsor:	Olema Pharmaceuticals
Development Phase:	Phase I Dose Escalation, Dose Expansion and Phase II
Sponsor's Medical Officers:	[redacted] Olema Pharmaceuticals, Inc. 512 2nd Street, 4th Floor San Francisco, CA 94107 [redacted] Olema Pharmaceuticals, Inc. 512 2nd Street, 4th Floor San Francisco, CA 94107
Protocol Amendment #6	28 June 2022
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Protocol Amendment #3	03 August 2021
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Protocol Amendment #1	13 May 2020
Original Protocol	13 April 2020

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Protocol Amendment #6 Date: **28 June 2022**

This protocol has been approved by Olema Pharmaceuticals, Inc. The following persons are authorized on behalf of Olema Pharmaceuticals, Inc. to approve this protocol and the signatures below document this approval.

[redacted]

[redacted]

3 SYNOPSIS

TITLE OF STUDY: 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 NUMBER: OP-1250-001	
STUDY SITES: Multiple centers in the United States (US), [redacted] and Australia	
STUDY PERIOD (MONTHS): Approximately 36 months	**PHASE OF DEVELOPMENT:** Phase I Dose Escalation/Dose Expansion and Phase II

STUDY DESIGN AND PLAN:

This is a Phase I dose escalation and dose expansion and Phase II monotherapy open--label, first--in--human study to determine the dose limiting toxicity (DLT), maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D), to characterize the safety and pharmacokinetic (PK) profile, and to estimate the preliminary anti-tumor activity of OP-1250 as a single agent in adult subjects with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative metastatic or locally advanced breast cancer. Treatment and study subject evaluation will be performed in 28-day cycles. This study comprises 2 Phases: Phase I (Part A [Dose Escalation] and Part B [Dose Expansion]) and Phase II. [redacted]

Phase I

Part A (Dose Escalation): This portion of the study will evaluate the safety and PK of a range of doses of OP-1250 administered orally daily to subjects and determine the MTD and/or RP2D. Part A will employ a rolling 6 dose escalation study design, whereby cohorts of 3 to 6 subjects will be sequentially enrolled and monitored for DLTs during the first cycle of study treatment.

Part B (Dose Expansion) 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 RP2D. Part B will enroll approximately 30 subjects in the expansion phase at the RP2D, or in the event 2 dose levels are being considered for the RP2D, then up to approximately 30 subjects will be enrolled in each of the 2 dose levels.

Phase II:

This portion of the study further explores the clinical activity, safety, and PK of OP-1250 at the RP2D and will estimate the preliminary anti-tumor activity. Subjects will be enrolled over 3 cohorts in the Phase II: Cohort A will enroll subjects with measurable disease without evidence of CNS metastases (subjects participating in Phase I, Part B (Dose Expansion) at the RP2D may be included in this cohort), Cohort B will enroll approximately 15 subjects with non-measurable (evaluable) disease without evidence of CNS metastases; and Cohort C will enroll approximately 15 subjects with evaluable disease (measurable and non-measurable) with CNS metastases.

Sub-Studies:

All subjects (Phase I and Phase II) will be eligible to participate in 1 of 2 sub-studies: Frequent ECG or Food Effect. Subjects may participate in either the Frequent ECG sub-study or the Food Effect sub-study but not both. Participation in a sub-study is optional.

STUDY ENDPOINTS:

The study objectives and endpoints of each of the 2 parts of the study are:

Phase I (Part A [Dose Escalation] and Part B [Dose Expansion])	
Primary Objectives	**Primary Endpoints**
• To identify the MTD and/or RP2D of OP-1250 (Part A [Dose Escalation]).	• Incidence and nature of DLTs as defined Section 8.8.2. • MTD and/or RP2D of OP-1250 when used as a single agent.
• To confirm the RP2D of OP-1250 (Part B [Dose Expansion]).	• RP2D of OP-1250 when used as a single agent.
• To assess the safety and tolerability of OP-1250 (Parts A [Dose Escalation] and B [Dose Expansion]).	• Incidence, nature, and severity of TEAEs and SAEs according to NCI-CTCAE version 5.0.
• To assess the PK of OP-1250 (Parts A [Dose Escalation] and B [Dose Expansion]).	• Plasma levels of OP-1250 at pre-defined intervals to establish PK parameters (including: C_{max}, C_{min}, T_{max}, AUC, $t_{½}$, and OP-1250 trough concentration at steady state).
Secondary Objectives	**Secondary Endpoints**
• To estimate the ORR defined as the CR + PR rate of OP-1250.	• ORR by evaluation of tumor response assessments using RECIST 1.1 in subjects with measurable disease.
• To estimate the CBR (CR + PR + SD ≥ 24 weeks) of OP-1250.	• 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]
Exploratory Objectives	**Exploratory Endpoints**
[redacted]	[redacted]

[redacted]	[redacted]
Phase II	
Primary Objectives	**Primary Endpoints**
• To estimate the ORR of OP-1250 in subjects with HR-positive/HER2-negative metastatic or locally advanced breast cancer with no evidence of CNS metastases who have progressed following at least 1 hormonal therapy regimen in the metastatic or locally advanced setting.	• ORR by evaluation of tumor response assessments using RECIST 1.1 in subjects without evidence of CNS metastases who have measurable disease.
• To assess the safety and tolerability of OP-1250.	• Incidence, nature, and severity of TEAEs and SAEs according to NCI-CTCAE version 5.0.
• To assess the plasma PK of OP-1250.	• Plasma levels of OP-1250 at pre-defined intervals to establish PK parameters (includes C_{max}, C_{min}, T_{max}, AUC, $t_{½}$, and OP-1250 trough concentration at steady state).
Secondary Objectives	**Secondary Endpoints**
• To estimate the CBR of OP-1250 in subjects with HR-positive/HER2-negative metastatic or locally advanced breast cancer with no evidence of CNS metastases who have progressed after receiving at least 1 hormonal treatment regimen in the metastatic or locally advanced setting.	• 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]	• [redacted]
Exploratory Objectives	**Exploratory Endpoints**
[redacted]	[redacted]

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

Abbreviations: AUC = area under the curve; C = Cycle; CBR = clinical benefit rate; C_{max} = maximum concentration; C_{min} = minimum concentration; CNS = central nervous system; CR = complete response; [redacted]; D = study day; DLT = dose-limiting toxicity; DoR = duration of response; EOT = end-of-treatment; [redacted]; ESR1 = estrogen receptor 1; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; iCBR = intracranial clinical benefit rate; MTD = maximum tolerated dose; mut = mutant; NCICTCAE = National Cancer Institute – Common Terminology for Adverse Events; ORR = overall response rate; PFS = progression-free survival; [redacted]; PR = partial response; [redacted]
RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase II dose; SAE = serious adverse event; SD = stable disease; $t_{1/2}$ = half-life; TEAE = treatment-emergent adverse event; T_{max} = time to maximum concentration; wt = wild-type

NUMBER OF SUBJECTS PLANNED:

Phase I: **Part A, Dose Escalation and Part B, Dose Expansion**: Approximately 42 subjects will be enrolled in Part A (Dose Escalation), and up to approximately 60 subjects will be enrolled in Part B (Dose Expansion). To allow for subject replacement, up to a total of approximately 102 subjects may be enrolled in the Phase I portion of the study.

Phase II: Up to 88 evaluable subjects will be enrolled over 3 cohorts in the Phase II: Cohort A will enroll 50 subjects with measurable disease without evidence of CNS metastases (subjects in the expansion at the RP2D will be included in this cohort), Cohort B will enroll approximately 15 subjects with non-measurable (evaluable) disease without evidence of CNS metastases; and Cohort C will enroll approximately 15 subjects with CNS metastases. To allow for subject replacement up to a total of approximately 88 subjects may be enrolled in the Phase II portion of the study.

[redacted]

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

Individuals eligible to participate in the Phase I Dose Escalation Phase and the Expansion Phase and the Phase II portion of the study must meet all of the following criteria:

Inclusion Criteria:

1) Age ≥ 18 years, including males and females.
2) Subject is willing and able to participate and comply with all trial requirements and to

provide signed and dated informed consent prior to initiation of any trial procedures.

3) Subject has histologically or cytologically confirmed locally advanced or metastatic breast cancer for which standard curative measures do not exist.

4) Tumor must be HR -positive and HER2 -negative as determined in the most recently obtained archival tumor tissue sample from a metastatic site (unless de novo diagnosis or no metastatic biopsy undertaken) using locally accepted criteria by the local pathology report. HR positive is defined as ER+/PR+, ER+/PR-, ER-/PR+.

5) [redacted]

6) The subject must have received at least 1 prior hormonal regimen for locally advanced or metastatic disease.

7) Subject must have received at least 6 months of a prior continuous endocrine therapy for locally advanced or metastatic breast cancer.

8) Subject has a life expectancy ≥ 6 months in the opinion of the investigator.

9) Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.

10) Females of childbearing potential must be willing to adhere to highly-effective contraception during the study and for 90 days following the last study drug administration:

a) Highly-effective contraception methods must include one of the following:

i) Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

ii) Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

iii) Male partner sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject and the success of the vasectomy must be medically confirmed as per local practice.

iv) Placement of a non-hormonal intrauterine device (IUD).

b) Additionally, females of childbearing potential, must meet all the following criteria:

i) Not pregnant, as confirmed by a negative serum pregnancy test (β-human chorionic gonadotropin) before starting study treatment.

ii) Not breastfeeding.

c) A female subject is considered to be of childbearing potential unless she meets one of the following criteria:

i) Is aged ≥ 60 years.

ii) Has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

iii) Has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone levels).

iv) Is menopausal (amenorrhea ≥ 12 months) while off drugs that interfere with ovarian function.

11) Male subject must be willing to adhere to highly-effective contraception during the study and for 90 days following the last study drug administration. Highly-effective contraception methods must include one of the following criteria:

a) Successful vasectomy.

b) For subjects who have not had a successful vasectomy, and are partners of women of childbearing potential, their partners adhere to any one of the following.

i) Hormonal contraception + male subject's use of a condom with spermicide.

ii) IUD (hormonal or non-hormonal).

iii) Bilateral tubal ligation + male subject's use of a condom with spermicide.

iv) Depo Provera + male subject's use of a condom with spermicide.

12) Pre and peri-menopausal female subjects must be willing to take a LHRH agonist ≥ 2 weeks before the first study drug administration and for the duration of the study.

13) Subjects must have not taken proton pump inhibitors (PPI) for 7 days prior to first study drug administration and agree to avoid taking PPI therapy for at least the first 2 cycles of therapy.

14) Subjects must have a corrected QT interval (QTcF) < 470 msec for females and < 450 msec for males (as calculated by the Fridericia correction formula).

15) Subjects must not have received prior hormonal therapy (including fulvestrant), CDK4/6 inhibitors, alpelisib, everolimus, or poly-ADP ribose polymerase (PARP) inhibitors within 2 weeks prior to the first administration of study drug.

16) Subjects must not have received prior chemotherapy within 2 weeks or investigational therapy within 4 weeks prior to the first administration of study drug or within 5 half lives of either chemotherapy or investigational agent (whichever is earlier). Subjects must not have received antibody therapy within 4 weeks prior to first administration of

study drug.

17) Prior radiotherapy must have been completed at least 2 weeks prior to start of Cycle 1 with recovery of any toxicities to ≤ Grade 1 (except for alopecia).

18) Subjects must have had at least 4 weeks from major surgery.

19) Subjects must have had any toxicities from prior therapy resolved or be ≤ Grade 1 as defined by NCI-CTCAE, v 5.0 at the time of starting study treatment with the exception of alopecia.

20) Subjects have the following laboratory values obtained ≤ 28 days prior to first dose (NOTE: if performed more than 3 days before the first study drug dose, then these laboratory tests need to be repeated within 3 days of C1D1 or pre-dose on C1D1 to ensure ongoing eligibility - with the exception of coagulation tests):

a) Serum creatinine ≤ the upper limit of normal (ULN) or has an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) formula.

b) Total bilirubin ≤ 1.5 × ULN unless prior history of Gilbert's syndrome.

c) Aspartate transaminase and alanine transaminase ≤ 2.5 × ULN, or ≤ 5 × ULN if due to liver involvement by tumor.

d) Hemoglobin ≥ 9.0 g/dL without requirement for red blood cell (RBC) transfusion within the last 4 weeks.

e) Platelets ≥100 × 10^9 cells/L.

f) Absolute neutrophil count (ANC) ≥ 1.5 × 10^9 cells/L (without the use of hematopoietic growth factors within the prior 3 weeks).

g) Prothrombin time (PT) and INR ≤ 1.5 × ULN, activated partial thromboplastin time (PTT) ≤ 1.5 × ULN. If on chronic anticoagulation, the INR must be in the therapeutic range.

Additionally, for individuals eligible to participate in Part A (Dose Escalation) of the Phase I portion of the study:

21) The subject must have received no more than 2 prior chemotherapy regimens for locally advanced or metastatic disease.

22) Subjects must have evaluable disease. Subjects with both measurable and non-measurable disease are eligible.

Additionally, for individuals eligible to participate in Part B (Dose Expansion) of the Phase I portion of the study and in the Phase II portion:

23) Subjects must have measurable disease by RECIST 1.1 criteria

24) The subject must have received no more than 1 prior chemotherapy regimen for locally advanced or metastatic disease.

25) The subject must have had at least 1 and no more than 4 prior hormonal based therapies for locally advanced, recurrent, or metastatic disease.

26) Subjects with brain metastases are eligible for the study (Phase I Part A, Phase I Part B, and Phase II Cohort C) if they meet all the following criteria:

a) The subject's brain metastases have been treated or do not require urgent local treatment at the time of study enrollment.

b) The subject has been off dexamethasone or is on a stable dose of dexamethasone of ≤ 2 mg daily (or an alternate steroid dosed at a level equal to ≤ 2 mg daily) for at least 2 weeks prior to first study drug administration.

Phase II Cohort A (measurable disease without evidence of CNS metastases):

27) Subjects must have measurable disease by RECIST 1.1 criteria.

28) Subject must not have evidence of CNS metastases. (Imaging of the brain is NOT required if the subject does not have symptoms suggesting CNS disease.)

Phase II Cohort B (non-measurable [evaluable] disease without evidence of CNS metastases):

29) Subjects must have non-measurable and evaluable disease.

30) Subject must not have evidence of CNS metastases. (Imaging of the brain is NOT required if the subject does not have symptoms suggesting CNS disease).

Additionally, for individuals eligible to participate in the Phase II Cohort C (CNS cohort)

31) The subject must have received no more than 3 prior chemotherapy regimens for locally advanced or metastatic disease.

32) The subject must have had at least one prior hormone-based therapy for locally advanced, recurrent, or metastatic disease.

33) Subjects must have evaluable disease. (Subjects with either measurable or non-measurable disease are eligible.)

Exclusion Criteria:

Individuals who meet any of the following exclusion criteria will not be eligible to participate in either the Phase I or Phase II part of the study:

1) Subjects with a prior or concurrent malignancy whose natural history or treatment may interfere with the safety or efficacy assessment of the investigational regimen as determined by the investigator.

2) Subjects with known impaired cardiac function or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, congestive heart failure (New York Heart Association Functional Classification Class 2B-4) and uncontrolled hypertension (defined as systolic blood pressure > 150 mm Hg and/or diastolic blood pressure

> 100 mm Hg on anti-hypertensive medications).

3) Subjects with myocardial infarction or unstable angina within 6 months prior to the first administration of study drug.
4) Subject with a history of cerebral vascular disease within 6 months prior to the first administration of study drug.
5) Subject has an active infection that requires antimicrobial therapy.
6) Subject has a history of leptomeningeal disease or spinal cord compression.
7) Subject has a history of allergic reactions attributed to compounds of similar chemical composition to OP-1250.
8) Subject has a history of a pulmonary embolism or deep venous thrombosis within the last 6 months or subject has an increased risk of thrombosis as determined by the investigator. (Subjects on chronic anticoagulation are allowed).
9) Medical history or ongoing gastrointestinal disorders that could affect absorption of OP-1250 (such as active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper GI surgery including gastric resection and including difficulties with swallowing capsules).
10) Subjects requiring therapy with strong CYP3A4 inhibitors and inducers.
11) Subjects requiring medications with known risk of QT interval prolongation or increased risk of Torsades de Pointes.
12) Subject has a known HIV infection.
13) Subject has a known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (eg, hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis.
14) Subject has clinically significant co-morbidities, such as uncontrolled pulmonary disease, CNS metastases that require treatment or steroid doses of > 2 mg, active infection, psychiatric disease, or any other condition that could impact the ability of the subject to participate in this study or otherwise has the potential to confound the study results.

INVESTIGATIONAL PRODUCT/STUDY TREATMENT:

OP--1250 will be supplied in tamper -resistant high density polyethylene (HDPE) bottles as capsules containing 15 mg or 60 mg dose strengths which the pharmacist or study staff will supply the appropriate dose for each dose cohort.

Dosing Regimen:

The starting dose is 30 mg once daily. OP-1250 will be administered orally once daily at approximately the same time of the day on an empty stomach. Subjects should be fasting for 2 hours prior to taking OP-1250 and for 1 hour post OP-1250 administration. For the first

2 cycles of therapy, subjects should take OP-1250 in the morning to allow for PK assessments. After the pre-dose PK sample is collected on C3D1, subjects may take OP-1250 at a time of day of their choosing, but should take the drug at approximately the same time each day. Cycles are repeated every 28 days. In cases where a subject misses his/her normal dosing time, the subject may still take the dose within 12 hours of the regular dosing time. Subjects should not take 2 consecutive daily doses within 12 hours of each other.

On days of in-clinic visits, OP-1250 will be administered to the subject by staff at the clinic (the subject should be counseled not to take their OP1250 dose at home on the day of the clinic visit).

[redacted]

Dose Levels:

Dose escalation for Phase I, Part A will be per the table below. Dose escalation will follow a rolling 6 design (Skolnik 2008).

The available safety and PK data will be reviewed, and intermediary dose levels may be tested. Up to a maximum dose of 360 mg once a day will be evaluated.

Phase I – Part A Dose Escalation: Dose levels OP-1250

Dose Level* Cohort #	Increase from Prior Cohort	Dose Level (mg)
-1	Not applicable	15
1	Not applicable	30
2	100%	60
3	100%	120
4	75%	210
5	43%	300
6*	20%	360

* Intermediate dose levels will be tested

Dose Escalation Plan for Phase I, Part A (Dose Escalation):

In Part A (Dose Escalation), cohorts of 3 to 6 subjects will be enrolled at each OP-1250 dose level and each subject will participate in only 1 cohort. Subjects at each dose level will be treated and observed for DLT through the end of the first cycle.

The rolling 6 dose escalation rules noted below will be employed, considering DLTs observed in Cycle 1. Cohorts of 3 to 6 subjects will be treated at each dose level. In the rolling 6 design, up to 6 subjects may be concurrently enrolled at each dose level of the study. The decision to escalate to the next highest dose level is made by the investigators participating in the Phase I study and representatives of the sponsor at a cohort review

meeting after at least 3 subjects have completed Cycle 1. Decisions as to whether to enroll a new subject onto the current, next highest, or next lowest dose level are made based on the number of DLTs and the review of AEs. Dose level assignment is based on the number of subjects currently enrolled in the cohort, the number of DLTs observed, the number of subjects at risk for developing a DLT (ie, subjects enrolled but who were not yet evaluable for toxicity), and the available PK results. If 2 or more DLTs at a given dose level are observed, the dose level will be de-escalated. Intermediate dose levels will be tested. Intra-subject dose escalation is not permitted during Part A (Dose Escalation).

Maximum Tolerated Dose Determination and Cohort Expansion

Number of Subjects with DLT at a Given Dose Level	**Escalation Decision Rule**
0 of 3, 4, 5 or 6	Enter 3 to 6 subjects at the next dose level.
≥2 of 3, 4, 5, or 6	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to 3 additional subjects will be entered at the next lowest dose level for a total of 6 subjects to be treated at that dose.
1 of 3, 4, or 5	Enter up to a total of 6 subjects at this dose level. If 1 of 6 subjects in this group experienced a DLT, then enter 3 to 6 subjects at the next dose level.
≤1 of 6 at highest dose level administered	**This is the MTD. The MTD is defined as the highest feasible dose tested in which fewer than 33% of subjects experienced DLT attributable to the study drug, when at least 6 subjects were treated at that dose and were assessable for toxicity.**

Definition of Dose Limiting Toxicity:

A Dose Limiting Toxicity (DLT) is defined as any of the following TEAEs that occur despite optimal medical management, 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.

- AST or ALT > 3× the ULN and a total bilirubin > 2× the 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 > 8× ULN or AST or ALT > 5× ULN for ≥ 14 days.
- ALT or AST > 3× 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 the same subject leading to DLT will be considered a single DLT.

Subjects in Part A (Dose Escalation) who are not DLT evaluable may be replaced as appropriate. DLT evaluable is defined as experienced a DLT and/or received at least 75% of the originally assigned doses in the first cycle. Subjects receiving less than 75% of the planned dose in Cycle 1 without a DLT will be evaluated in the overall safety analysis, but not for the purposes of dose escalation.

***Definition of MTD*:**

For purposes of defining the MTD and/or expansion phase recommended dose of OP-1250, subjects will be evaluated according to the actual starting dose of OP-1250 during the first treatment cycle. For most subjects, this will be the dose cohort to which they were assigned. Subjects who receive at least 75% (21 days) of the planned doses in Cycle 1 will be considered to have sufficient safety data/follow-up to support dose escalation. Subjects who withdraw from study before receiving 75% of the planned doses in the first cycle of treatment for reasons unrelated to study drug toxicity will be considered to have inadequate data to support dose escalation. In such cases, replacement subjects may be enrolled to receive the same starting dose of OP-1250 as the subjects who withdraw prematurely.

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

***Determination of RP2D*:**

Following Phase 1a dose escalation of OP-1250 from 30 mg to 300 mg QD, a recommended phase 2 dose (RP2D) range was defined of 60 to 120 mg QD. Sixty patients are planned for Phase 1b enrollment, with 30 patients at each dose level (60 and 120 mg). At 60 mg and 120 mg, OP-1250 demonstrated high oral bioavailability and dose proportional exposure. At 120 mg, OP-1250 consistently exceeded the predicted efficacy plasma concentration thresholds from preclinical models. Safety data from 37 patients enrolled in Phase 1b indicated no clinically meaningful difference in the frequency of TEAEs between the 2 dose levels (60 mg, 120 mg) as the most common

TEAEs (≥10%) were nausea (28%, 21%), vomiting (17%, 16%), fatigue (17%, 5%), and headache (11%, 11%), respectively. Most events were Grade 1 or 2, with the exception of two Grade 3 events at 60 mg (diarrhea and anemia). There were no dose reductions or dose discontinuations due to an AE. Based on safety and pharmacokinetic data from Study OP-1250-001,120 mg OP1250 QD has been selected as the RP2D.

Since the RP2D has been determined, active subjects enrolled on the Phase I part of the study may be treated at the RP2D with approval of the Medical Monitor if the investigator or designee considers this in the best interest of the subject after discussion with the Medical Monitor.

Dose Modifications for Phase I and Phase II:

All AEs should be assessed according to the CTCAE, v5.0. In event of multiple toxicities, dose delays and modifications should occur in accordance with the highest grade AEs observed.

Subjects who experience a DLT or any of the protocol-defined AEs in Cycle 2 and beyond will have study drug treatment interrupted. Dose modification guidelines will include dose reductions as follows: the first dose reduction will be approximately 20% to 30%, the second dose reduction is approximately 40% to 50%, and the third dose reduction is approximately 70% to 80%. Dose reductions below 15 mg daily are not allowed. Dose modifications will only be made for TEAEs that are not clearly due to disease progression or extraneous causes.

CONCOMITANT MEDICATIONS

All prescription and over-the-counter medications taken by a subject within 30 days before the first study drug administration will be recorded in the designated electronic CRF (eCRF).

The following actions should be considered with the following medications/therapies:

- PPIs should be avoided and are prohibited during the first 2 cycles of therapy. After that, PPI may be used only if other methods of symptom control have been ineffective. The Medical Monitor should be notified if PPI are started. The use of H2 blockers is strongly discouraged. If the subject experiences symptoms of gastric acid reflux that are not relieved with conservative measures (small meals, no eating after 6 PM, avoiding foods that stimulate stomach acid such as caffeine, alcohol, tomatoes, spicy foods), the investigator or designee may prescribe H2 blockers to be taken once or twice a day provided they are taken at least 2 hours prior to (or post) the OP-1250 dose; however, 4 hours is preferred.
- No other cancer therapies or investigational agents are permitted during the entire duration of the study treatment.

Based on the in vitro drug-drug interaction profile of OP-1250, the types of concomitant medications to avoid or to use with caution:

Concomitant Medication Types	OP-1250 Characteristic	Potential Effects of Co-Administration	Approach
Prolongs QT	Unknown	Possible increased risk of Torsades de Pointes	Avoid (see Appendix C)
Strong CYP3A4 Inhibitors or Inducers	Metabolized primarily by CYP3A4	OP-1250 levels may be increased if administered with CYP3A4 inhibitors or decreased with CYP3A4 inducers	Avoid (see Appendix B)
P-gp substrates and BCRP substrates	Potential inhibitor of intestinal P-gp	May increase drug levels of concomitant medications that are substrates for intestinal P-gp (eg, digoxin) and BCRP substrates (eg, sulfasalzaine)	Use P-gp and BCRP substrates with narrow therapeutic index with caution (see Appendix D)
Substrates of CYP2C8 and CYP2C9	Potential time dependent inhibitor of CYP2C8 and CYP2C9	May increase drug levels of concomitant medications that are substrates for CYP2C8 (eg, repaglinide) or CYP2C9 (eg, [S]-warfarin)	Use CYP2C8 and CYP2C9 substrates with narrow therapeutic indexwith caution (see Appendix D)
PPIs and H2 Blockers	Absorption may be affected by gastric pH.	Co-administration may affect the absorption of OP-1250	PPIs should be avoided and are prohibited during the first 2 cycles of therapy. The use of H2 blockers is strongly discouraged. (See the first bullet point of Section 8.13 for full details.)

Abbreviations: CYP = cytochrome P450 isozyme; H2 = histamine 2 receptor; P-gp = P-glycoprotein; PPI = proton pump inhibitor

Although in vitro, OP-1250 appears to be a substrate, primarily, of CYP3A4 and as such its exposure may be increased by CYP3A4 inhibitors (eg, itraconazole) and reduced by CYP3A4 inducers (eg, rifampin), results from in vivo studies are not yet available. Therefore, subjects should avoid strong CYP34A inhibitors or inducers if possible. However, their use in this study is not exclusionary.

Pre- and perimenopausal women must take an LHRH agonist of physician's choice.

Medications for nausea, vomiting, diarrhea, and constipation may be given according to the standard of care guidelines at the discretion of the investigator or designee. Granisetron (or other) is preferred over ondansetron due to the potential prolongation of the QT interval with ondansetron.

Bisphosphonates or other bone modifying agents are allowed provided the subject has been on these agents for at least 4 weeks prior to Cycle 1.

Subjects who have febrile neutropenia (FN) should receive antibiotics per standard of care. G-CSF may be used at the investigator or designee's discretion.

Other medications considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded in the eCRF.

DURATION OF TREATMENT:

In the absence of unacceptable OP-1250 treatment-related toxicity or disease progression, subjects may receive OP-1250 treatment for up to 1 year and beyond 1 year with the agreement of the investigator or designee and the sponsor.

Treatment will continue until any 1 of the following occurs:

- SAE or AE that require dose discontinuation.
- Progressive disease as determined by RECIST 1.1. (Tumor marker elevations in the absence of unequivocal radiologic progression of target or non-target lesions is not considered disease progression. Per RECIST 1.1, disease progression requires an overall disease burden increase based on the change in non-measurable disease that is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume,' which is equivalent to a 20% increase in diameter in a measurable lesion.)
- Initiation of non-protocol anticancer therapy.
- Illness or condition that may interfere with the subject's participation or require treatment discontinuation.
- Treating investigator or designee's determination that continuation of protocol therapy is not in the subject's best interests.
- Pregnancy.
- Noncompliance.
- Voluntary withdrawal of consent.
- Sponsor termination of the study.

REFERENCE THERAPY(IES), DOSE, ROUTE AND REGIMEN:

None

CRITERIA FOR EVALUATION:

Safety:

Safety will be assessed by periodic physical examinations, 12-lead electrocardiograms (ECGs), clinical laboratory assessments, and monitoring of AEs. 12-lead ECGs will be evaluated at baseline (Screening) and at prespecified timepoints during treatment and at the end of treatment. Additional clinical laboratory assessments and 12-ECGs will also be

obtained when clinically indicated. AEs will be graded using NCI-CTCAE version 5.0 criteria.

Site teleconferences between the sponsor and all participating sites will be held during the dose escalation phase to discuss any suspected AEs/DLTs that have occurred in each cohort. The Safety Committee will include the investigator(s) participating in the study, the Medical Monitor, and the sponsor's Medical Director. Study drug-related toxicities from the current cohort will be reviewed during the site teleconferences before escalating to the next dose level.

PK and ECG Determinations:

The PK profile will be assessed by determining the plasma levels of OP-1250 at the intervals indicated below. In addition to the scheduled samples, an unscheduled PK blood sample should be drawn as soon as possible after a SAE and following a dose reduction of OP-1250. Following a dose reduction, the pre-dose sample will be collected at the next clinic visit that is least 1 week after the subject has taken OP-1250 at a reduced dose.

All subjects will have ECGs in triplicate at multiple timepoints.

Subjects should be supine for 10 minutes before obtaining the ECG and 2 to 5 minutes should elapse between each ECG. The ECG should be obtained immediately prior to PK blood draws and prior to assessment of blood pressure and other vital signs.

[redacted]

Efficacy:

Radiographic and/or physical assessments of the malignancy will be made at Screening/baseline (within 28 days prior to 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 radiographic assessment following the completion of 8 cycles of therapy. Overall response (CR and PR) as determined by the subject's best tumor response, [redacted] will be assessed using RECIST 1.1. For subjects with brain metastatic disease enrolled in the study, assessment of response rate in the non-CNS and CNS compartments will be defined according to RECIST 1.1 [redacted]

[redacted] CBR will be determined as follows: CR + PR + subjects with SD for ≥ 24 weeks. iCBR will be determined as follows: intracranial CR + intracranial PR + subjects with intracranial SD for ≥ 24 weeks in the CNS.

STATISTICAL METHODS:

Safety Analyses:

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, DLTs, laboratory values, electrocardiogram results, vital signs, and ECOG PS. Safety data analysis will be conducted on all subjects receiving at least 1 full or partial dose of OP-1250. DLT summary will be conducted on DLT evaluable subjects, defined as subjects in the dose escalation portion of the study receiving at least 75% of OP-1250 doses or experience a DLT in Cycle 1. All treatment-emergent AEs regardless of attribution will be summarized by cohort, as follows:

- All DLTs (regardless of grade).
- All AEs (regardless of grade or attribution).
- All Grade 3/4/5 AEs.
- All drug-related AEs (regardless of grade).
- All AEs leading to study drug or study discontinuation.
- All SAEs, including deaths.
- All AEs of special interest (regardless of grade).

A separate listing of all on-study deaths will be presented.

Efficacy Analyses:

An analysis of ORR will be conducted for subjects with measurable disease enrolled in the study who have completed at least 1 cycle of OP-1250 and have a post-treatment tumor assessment. The number and percentage of subjects experiencing an overall response (CR + PR) will be summarized. [redacted]

CBR will be summarized based on the percentage of subjects experiencing clinical benefit (ie, CR + PR + SD ≥ 24 weeks).

Subjects without measurable disease will not be included in the determination of ORR; however, they will be included in safety, secondary, and exploratory analyses where appropriate.

Subjects with CNS metastases will be analyzed in a separate cohort. ORR in subjects with CNS metastases will be performed using both RECIST 1.1 (for disease in the CNS and non-CNS components) [redacted]

[redacted]

Pharmacokinetic Analyses:

Pharmacokinetic parameters will be determined for the PK Analysis Set using standard compartmental or non-compartmental methods. A listing of subjects excluded from the analysis set and individual data points excluded from the analysis will be provided. The final analysis of PK parameters will be calculated based on actual sample collection time, rather than scheduled times. In addition, the PK sparse exposure data from this study may be used in the development of population PK and PK/PD models. Pharmacokinetic plasma levels and parameters will be determined, listed, and summarized for the PK evaluable population in the Pharmacokinetic Analysis Plan (PKAP). Only samples with acceptable PK (as defined in the PKAP) will be included in the summary statistics, and a listing of individual data points that were excluded from the analysis will be presented. Plasma concentrations will be listed by for the PK Population. Summary statistics of OP-1250 concentrations will be reported by dose level, Day and Cycle. Details of this analysis will be provided in the PKAP. Possible relationships between PK parameters, PD variables, safety, and efficacy may be examined.

[redacted]

[redacted]

3.1 Schedules of Events

Table 1: Schedule of Events for All Subjects

Assessments	Screening	Treatment Period (28-Day [4-Week] Cycles)													EOT Visit	Safety Follow-up
	≤ 28 days	C1					C2				C3 and subsequent odd Cycles		C4 and subsequent even Cycles		Within 42 days after last IP dose	At 30 to 42 days after EOT Visit
		D1	D2	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D15		
Visit window				± 2 d	± 2 d	± 2 d	± 2 d	± 2 d	± 2 d	± 2 d	± 5 d	± 2 d	± 5 d	± 2 d		
General eligibility/safety assessments																
Obtain informed consent	X															
Medical history	X															
Demographics	X															
Physical examination[1]	X	X		X	X		X		X		X		X		X	
ECOG performance status	X	X		X	X		X				X		X		X	
Vital signs, height[2],weight	X	X		X	X		X				X		X		X	
Triplicate 12-lead ECG[3]	X	X	X	X	X		X				X (C3, C5, C7, C9 only)					
AE recording[4]		X	X	X	X		X		X		X		X		X	X
Prior and concomitant medications and therapies[5]	X	X	X	X	X		X		X		X		X		X	
Investigational product																
Dispensing and compliance check of OP-1250 and drug diary			X	X	X		X		X		X		X			
OP-1250 return and compliance check				X	X		X		X		X		X		X	
OP-1250 administration in clinic at study site		X	X	X	X		X		X		X		X			

Assessments	Screening	Treatment Period (28-Day [4-Week] Cycles)													EOT Visit	Safety Follow-up
	≤ 28 days	C1					C2				C3 and subsequent odd Cycles		C4 and subsequent even Cycles		Within 42 days after last IP dose	At 30 to 42 days after EOT Visit
		D1	D2	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D15		
Visit window				± 2 d	± 2 d	± 2 d	± 2 d	± 2 d	± 2 d	± 2 d	± 5 d	± 2 d	± 5 d	± 2 d		
Laboratory assessments																
Pregnancy test (WOCBP only)[6]	X	X					X				X		X		X	
Hematology[7] and serum chemistry[8]	X	X		X	X	X (CBC only)	X	X (CBC only)	X	X (CBC only)	X	X (C3 only; CBC only)	X	X (C4 only; CBC only)	X	
Fasting lipid profile[9]	X										X (C3/C5 only)					
Coagulation	X										X (C3/C5 only)					
Urinalysis[10]	X															
OP-1250 PK[11]		X	X	X	X		X				X (C3, C5, C7, C9 only)					
[redacted]	X															
[redacted]	X										X (C3 only)				X	
Biopsy and disease assessment																
Radiology examination[14]	X										X[17]				X[18]	
Tumor measurement	X										X[17]				X[18]	
[redacted]	X	X									X (C3 only)				X	
Safety follow-up																
Safety (telephone or in person) follow-up[16]																X

Abbreviations: AE = adverse event; C = cycle; CBC = complete blood count; CT = computed tomography; [redacted] d = day; D = study day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; h = hour(s); End-of-treatment = EOT; IP = investigational product; MRI = magnetic resonance imaging; PK = pharmacokinetic; WOCBP = women of child-bearing potential

[1] Complete physical examination will be done at Screening and during the EOT visit. Symptom directed physical examination will be done at every visit, with exception C1D2 where no physical examination is required.

[2] Height is only needed at Screening (baseline).

[3] At each time point, 3 consecutive 12-lead ECGs will be performed 2 to 5 minutes apart to determine mean QTc. See ECG sampling schedule in Table 2 for all subjects, [redacted]

[4] Adverse events will be recorded after administration of the first dose of study drug (AEs reported between signing the informed consent form and before C1D1 dose administration will be captured as medical history). All related AEs will be followed to resolution, stabilization, or loss of contact with the subject. All unrelated AEs will be followed until the time of the Safety Follow-up visit, which is between 30 to 42 days after the EOT visit.

[5] Concomitant medications, including vaccinations, will be recorded from 30 days prior to C1D1 dose until the EOT visit. All prior anti-cancer therapies (chemotherapy, antibody, and hormonal therapies) are required to be recorded by line of therapy.

[6] Serum pregnancy test will be done at Screening/baseline. Either serum or urine pregnancy test will be done within 3 days prior to C1D1 and every cycle thereafter and at the EOT visit.

[7] Hematology (CBC with differential, platelets, and hemoglobin) will be done within 3 days prior to the C1D1 visit and results checked against eligibility criteria prior to dosing at Cycle 1. When noted as "CBC only," all hematology tests are to be performed.

[8] Chemistry (blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, and glucose) will be done within 3 days prior to the C1D1 visit and results will be checked against eligibility criteria prior to dosing at Cycle 1.

[9] Fasting lipid panel includes total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.

[10] Macroscopic assessment of the amount of protein, glucose, white blood cells, and blood (levels should be recorded if available) and microscopic analysis if abnormality is noted.

[11] See PK sampling schedule in Table 2 for all subjects, [redacted]

- [redacted]
- [redacted]

[redacted]

[14] Baseline CT (with contrast) or MRI of chest, abdomen, and pelvis must be obtained within 4 weeks prior to the first IP dose. The same method (CT with contrast or MRI) must be used throughout the study. Subjects with brain metastasis should have MRI scans of the brain.

[redacted]

[16] Safety follow-up is to occur at 30 to 42 days after EOT visit. All related AEs will be followed to resolution, stabilization, or loss of contact with the subject. All unrelated AEs will be followed until the time of the Safety Follow-up visit, which is between 30 to 42 days after the EOT visit.

[17] Radiographic assessment (and physical assessments of malignancy) should be performed at every 2 cycles starting at C3 (ie, C5, C7, C9, etc). Assessments must be performed prior to commencing treatment for that cycle. Post C9 assessment, for subjects who have been determined to have obtained a clinical benefit from OP-1250 may reduce frequency of assessments to every 3 cycles (ie, C12, C15, C18, etc.) prior to commencing treatment for that cycle.

[18] Tumor assessments are to be performed on subjects who have not previously shown radiologic progression.

Table 2: Pharmacokinetic and Electrocardiogram Sampling Schedule for All Subjects[1]

Visit Identifier	C1								C2							C3, C5, C7, and C9	Unscheduled[5]
Study Days	D1 and D8[3]							D2 and D15	D1							D1	
Hours before/after dose and allowed window (± min)	Pre-dose (- 15)	0	0.5 (± 15)	1 (± 15)	2 (± 30)	4 (± 30)	6 (± 30)	Pre-dose (- 15)	Pre-dose (- 15)	0	0.5 (± 15)	1 (± 15)	2 (± 30)	4 (± 30)	6 (± 30)	Pre-dose[4] (- 15)	
Study treatment administration		X								X							
PK blood sampling	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X
12-lead ECG[2]	X					X Day 1 only		X	X					X		X	X

Abbreviations: C = cycle; CNS = central nervous system; D = study day; ECG = electrocardiogram; PK = pharmacokinetic; QTcF = QT interval corrected by the Fridericia correction formula; SAE = serious adverse event

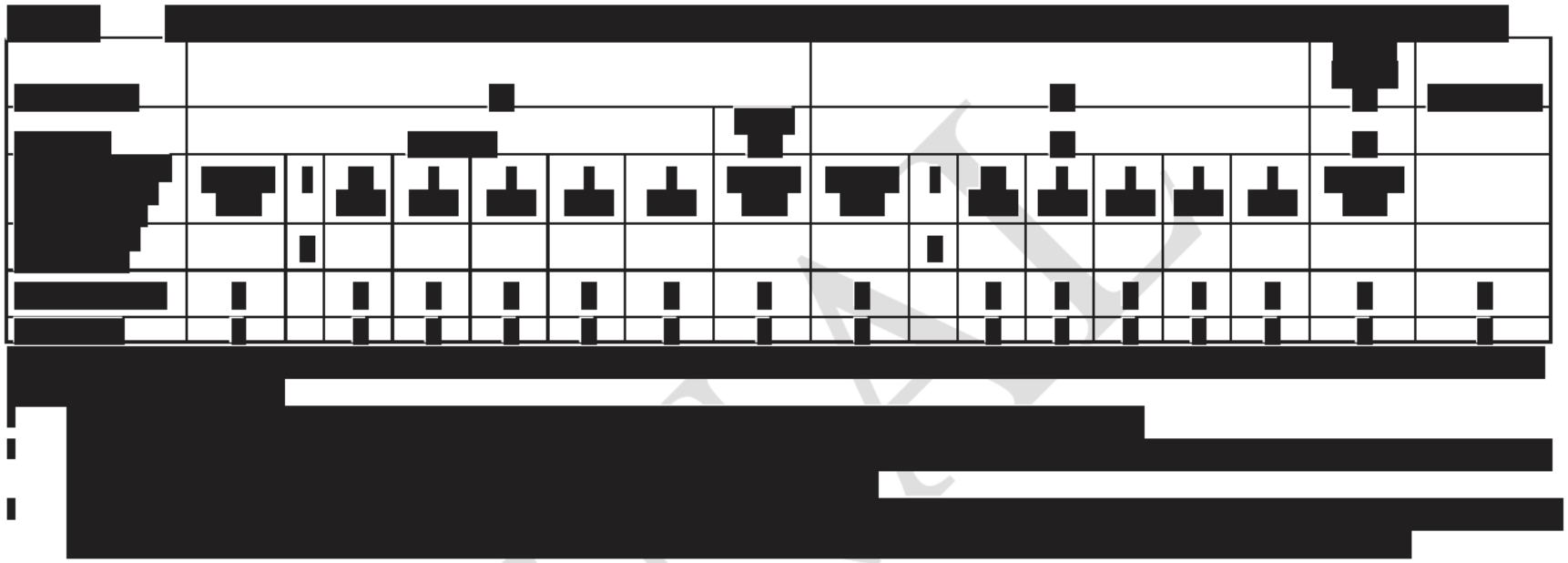
1 [redacted]

2 At each time point, 3 consecutive 12-lead ECGs will be performed 2 to 5 minutes apart to determine mean QTc.

3 C1D8 post-dose PK assessments may be omitted for subjects in Phase II Cohort A (measurable disease without CNS metastasis) and Cohort B (non-measurable disease without CNS metastasis). C1D8 post-dose PK assessments are required for subjects in Phase I and Phase II Cohort C (CNS metastasis).

4 For subjects who elect to take OP-1250 at a time other than the mornings for C3 and beyond, the pre-dose PK sample and ECG should be at least 16 hours after OP-1250 dosing and the time of dosing should be recorded in the subject diary.

5 In addition to the scheduled PK sampling and ECG schedule, an unscheduled PK sample and ECG should be collected pre-dose as soon as possible after a SAE, and if OP-1250 is dose reduced pre-dose at the next clinic visit (at least a week after the subject has taken OP-1250 at a reduced dose).



[redacted]

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5 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	Adverse event
[redacted]	[redacted]
AF	Activation function
AI	Aromatase inhibitors
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
BUN	Blood Urea Nitrogen
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
CBC	Complete Blood Count
CBR	Clinical benefit rate
CDK	Cyclin dependent kinase
CERAN	Complete Estrogen Receptor ANtagonist
CFR	Code of Federal Regulations
[redacted]	[redacted]
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DLT	Dose Limiting Toxicity
DLTAS	Dose Limiting Toxicity Analysis Set
[redacted]	[redacted]
DPA	Data Protection Act
EC	Ethics Committee
ECGs	Electrocardiograms

ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EFS	Efficacy Analysis Set
EGFR	Epidermal Growth Factor Receptor
EOT	End-of-treatment
ER	Estrogen receptor
ESMO	European Society of Medical Oncology
ESRα	estrogen receptor alpha
ESR1	*Estrogen Receptor 1 (ESR1)*
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FN	Febrile neutropenia
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
GLP	Good laboratory practice
GPP	Good Publication Practice
HDL-C	High Density Lipoprotein Cholesterol
HED	Human equivalent dose
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HR	Hormone receptor
IB	Investigator's Brochure
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IGF	Insulin-like growth factors
IND	Investigational New Drug
INR	International normalized ratio
IP(s)	Investigational Product(s)
IRB	Institutional Review Board

IV	Intravenous, Intravenously
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
LHRH	Luteinizing hormone-releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MRI	Magnetic Resonance Imaging
MRSD	Maximum recommended starting dose
MTD	Maximum Tolerated Dose
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	Overall response rate
PARP	Poly-ADP ribose polymerase
PD	Progressive disease
PDX	patient-derived xenograft
PE	Physical Examination
[redacted]	[redacted]
PIC	Subject Informed Consent
PI3Ks	Phosphoinositol-3-Kinases
PI3KCA	Phosphoinositide 3-kinase Alpha Catalytic Subunit
PK	Pharmacokinetic
PKAB	Pharmacokinetic Analysis Plan
PKAS	Pharmacokinetic Analysis Set
PPI	Proton pump inhibitor
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	QT corrected
QTcF	QT interval corrected by the Fridericia correction formula
[redacted]	[redacted]
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
SAE	Serious Adverse Event

SAF	Safety Analysis Set
SD	Stable disease
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulators
STD_{10}	Severely Toxic Dose to 10% of rats
$T_{1/2}$	Half-life
TDE	Target dose exposure
TEAE	Treatment-emergent adverse event
T_{max}	Time of Maximum Concentration
ULN	Upper Limit of Normal
US	United States
WOCBP	Woman of child-bearing potential

Definition of Terms:

Investigational Product (IP) or Study Drug:

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use." (from E6 International Conference on Harmonisation [ICH] 1.33)

The terms "IP" and "study drug" may be used interchangeably in the protocol.

6 INTRODUCTION

6.1 Background Information on Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women. Around 5% to 10% of cases are metastatic at diagnosis, and close to 30% of patients with early stage disease will go on to relapse and develop metastatic disease (Reinert 2015; Sini 2016). It was estimated that 150,000 women were living with metastatic breast cancer in the United States (US) in 2017. (Mariotto 2017) Hormone receptor -positive and HER2 -negative is the most common subtype of metastatic breast cancer, representing roughly 70% of all cases.

Endocrine therapy forms the cornerstone of treatment for advanced -stage HR -positive and HER2-negative breast cancer and several endocrine agents are available for the treatment of this subtype of breast cancer. Endocrine therapy is the standard of care for the initial treatment of HR-positive and HER2-negative breast cancer due to its favorable toxicity profile when compared with chemotherapy. However, development of endocrine resistance is inevitable, requiring multiple sequential lines of therapy. (D'Souza 2018) Eventually, endocrine therapy is no longer effective, and chemotherapy is warranted. There is an unmet need for effective endocrine agents in the third and subsequent lines of therapy.

For over 40 years, single ag-ent endocrine therapy was used as initial therapy for HR -positive metastatic breast cancer. Tamoxifen was first used for the treatment of advanced breast cancer in the 1970s. Third -generation aromatase inhibitors (AIs) became available in the 1990s and rapidly became the mainstay of treatment in both the first- and second -line settings. In 2002, fulvestrant, the first selective estrogen receptor degrader (SERD) to be approved by the Food and Drug Administration (FDA), became available. Fulvestrant is currently used in the management of metastatic HR-positive breast cancer in both the first- and subsequent-line settings.

Unfortunately, the majority of patients with HR-positive and HER2-negative metastatic breast cancer will develop endocrine resistant disease. Endocrine resistance can be either de novo, or acquired. The European Society of Medical Oncology (ESMO) defines primary endocrine resistance as relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease (PD) within the first 6 months of first-line endocrine therapy for advanced breast cancer while on endocrine therapy. Secondary endocrine resistance is defined as relapse while on adjuvant endocrine therapy but after the first 2 years, or relapse within 12 months of completing adjuvant endocrine therapy, or PD ≥6 months after initiating endocrine therapy for advanced breast cancer, while on endocrine therapy (Cardoso 2018).

Multiple therapeutic options, including CDK4/6, mTOR, and PI3K inhibitors to be used in combination with endocrine therapy, have been developed to overcome endocrine resistance (Sini 2016). In 2012, everolimus, an inhibitor of mammalian target of rapamycin (mTOR), was approved for use in combination with exemestane for the treatment of metastatic breast cancer that had progressed following a non-steroidal AI. However, the use of everolimus has been limited due to its modest activity and less tolerable adverse effect profile. A major advance in the treatment of metastatic HR-positive and HER2-negative metastatic breast cancer occurred in 2015 with the development of CDK 4/6 inhibitors for use in combination

with endocrine therapy (Turner 2015). Currently, several different CDK4/6 inhibitors (including palbociclib, ribociclib, abemaciclib) are available for use in combination with endocrine therapy in either the first- or second-line settings. (D'Souza 2018) The National Comprehensive Cancer Network (NCCN) guidelines recommend endocrine therapy in combination with a CDK4/6 inhibitor for the treatment of HR-positive and HER2-negative metastatic breast cancer in the first- or second-line setting (NCCN guidelines Breast Cancer Version 3.2020). However, the optimal sequencing of endocrine therapies in advanced breast cancer is not known. As illustrated in a review by D' Souza, (D'Souza 2018), a common sequence is first-line CDK4/6 inhibitors plus an AI (median progression free survival [PFS] > 24 months; Finn 2016), second line fulvestrant (median PFS approximately 6.5 months; Di Leo 2010) and third line mTOR plus AI (median PFS 6.9 months in the everolimus arm and 2.8 months in the exemestane alone arm; Baselga 2012). Another sequence of endocrine therapies is first-line AI or fulvestrant (median PFS 13-16.6 months; Robertson 2016), second-line CDK4/6 + fulvestrant (approximate median PFS 16 months; Turner 2015) and third line everolimus plus exemestane (PFS 6.9 months for the everolimus-exemestane vs 2.8 months exemestane alone; Baselga 2012). Taken together, these data show that first-line treatment with a CDK4/6 inhibition in combination with hormonal therapy results in significant improvement in PFS; however, the total PFS is similar regardless of the sequencing. What is clear, however, is that PFS in HR-positive/HER2-negative breast cancer decreases with subsequent lines of therapy, as tumors acquire resistance to endocrine therapy. Another class of agents that may be useful in overcoming endocrine resistance in advanced breast cancer are the phosphoinositol-3-kinases (PI3K) inhibitors. The PI3K-AKT-mTOR pathway is a frequently activated signaling pathway in breast cancer. Inhibition of PI3K may help restore sensitivity to other therapies when used in combination regimens. Alpelisib in combination with fulvestrant was FDA-approved in 2019 for the treatment of postmenopausal women and men with estrogen receptor (ER)+, HER2-negative, and phosphoinositide 3-kinase alpha catalytic subunit (PIK3CA) mutated advanced breast cancer following progression on or after an endocrine based regimen. The SOLAR-1 trial reported a PFS of 11.0 months in the alpelisib-fulvestrant group, as compared with 5.7 months in the placebo–fulvestrant group (André 2019). Although some progress has been made with combination therapy using agents targeting the PI3K-AKT-mTOR pathway (everolimus and alpelisib), the adverse effect profile of these drugs is intolerable for up to 25% of patients. In BOLERO-2, 19% of subjects discontinued everolimus due to adverse effects; in SOLAR-1, 25% of subjects on the alpelisib-fulvestrant arm discontinued therapy due to adverse events (AEs).

Although estrogen receptor alpha (ESRα) mutations are uncommon in primary, treatment naïve tumors, as many as 20% to 40% of women previously treated with AIs and/or fulvestrant for metastatic breast cancer have measurable activating mutations detectable upon progression (Spoerke 2016, Jeselsohn 2014, Robinson 2013, Toy 2013). Somatic ESRα mutations in patients with metastatic breast cancer may promote estrogen-independent activation of the receptor and endocrine resistance. The degree to which all recurrent mutants can drive estrogen-independent activities and reduced sensitivity to ER antagonists has not been established. Less toxic effective therapies are needed for the treatment of endocrine resistant metastatic breast cancer, including patients with activated ER mutations, particularly

in third and later line therapies. Therapy for late-line treatment of endocrine resistant breast cancer is an unmet clinical need.

6.2 OP-1250

OP-1250 is a small molecule complete estrogen receptor antagonist (CERAN). OP-1250 potently competes with the endogenous activating estrogenic ligand 17-beta estradiol for binding in the ligand binding pocket. OP-1250 blocks estrogen-driven transcriptional activity, inhibits estrogen-driven breast cancer cell growth, and induces degradation of the ER. CERANs both completely inactivate ER and degrade ER, unlike some SERDs that only degrade ER or selective estrogen receptor modulators (SERMs), which have mixed agonist and antagonist effects. OP-1250 completely inactivates ER by inactivating both the activation function 1 (AF1) and activation function 2 (AF2) transcriptional activation functions. OP-1250 robustly degrades the estrogen receptor in ER+ cell lines. In vivo studies demonstrate that OP-1250 has no agonist activity in the immature ovariectomized mouse uterus and blocks estrogen-driven uterine weight increase.

OP-1250 blocks estrogen-driven proliferation of ER+ cancer cells lines. Partial antagonists (including SERM/SERDS) stimulate proliferation of CAMA-1 human breast cancer cells even in the absence of estrogen. In contrast, OP-1250 fully blocks estrogen-driven proliferation of CAMA-1 breast cancer cells. OP-1250 shows superior efficacy to other SERM/SERDs in blocking proliferation of HCC-1500 breast cancer cells in culture. The superior efficacy of OP-1250 is considered to be due to its ability to completely antagonize ER, (as opposed to partial antagonism seen with other SERMs/SERDs).

OP-1250 is highly effective in xenograft models of human breast cancers (both wild-type and mutant ER) implanted into nude mice, with activity at doses as low as 0.3 mg/kg daily and demonstrates tumor shrinkage at doses as low as 3 mg/kg daily in patient-derived xenograft (PDX) models with wild-type ER. In PDX studies using a tumor that carries Y537S mutant ERα, the daily dose of 10 mg/kg of OP-1250 elicited the maximum efficacious outcome, which was shrinkage of the tumors of more than 50%.

OP-1250 is orally bioavailable and has a long half-life in all species tested to date, including the mouse, rat, dog, and cynomolgus monkeys. These data suggest that administration of OP-1250 will give high and sustained drug exposure in humans with once daily dosing. OP-1250 penetrates rodent brains. It is highly protein bound. The fraction of unbound OP-1250 in mouse plasma was determined to be approximately 0.08%.

In vitro, OP-1250 inhibits CYP2C8 and CYP2C9 in a time-dependent manner and may reduce the clearance of CYP2C8 substrates (eg, repaglinide) and CYP2C9 substrates (eg, [S]-warfarin). At clinically relevant concentrations, OP-1250 does not induce drug metabolizing enzymes.

OP-1250 may inhibit P-gp (P-glycoprotein) and breast cancer resistance protein (BCRP) in the intestine and increase the bioavailability of P-gp substrates (eg, digoxin) and BCRP substrates (eg, sulfasalazine). The P-gp and BCRP inhibition of OP-1250 is limited to the intestine and OP-1250 is not an inhibitor of other common drug transporters. OP-1250 is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, or OCT1.

In vitro, OP-1250 appears to be a substrate, primarily of CYP3A4, and as such its exposure may be increased by strong CYP3A4 inhibitors (eg, itraconazole) and reduced by strong CYP3A4 inducers (eg, rifampin). OP-1250 is poorly soluble at a high pH but is freely soluble at a pH of 3. Because of the pH-dependent solubility of OP-1250, in this initial study, agents such as proton pump inhibitors (PPIs) should be avoided because they increase the normal acid pH of the stomach and may affect the pharmacokinetics (PK) of OP-1250. The bioavailability of OP-1250 when combined with drugs that affect gastric pH is being determined in a study of healthy volunteers. OP-1250 was evaluated in a comprehensive preclinical toxicology program in rats and dogs dosed for up to 28 days. OP-1250-related toxicities were dose-related and consistent with systemic exposure.

Most OP-1250 -related findings were consistent with the pharmacological mechanism, antagonism of ER. Since OP-1250 targets a hormone pathway, it is expected for OP-1250 to have a variety of effects in healthy animals. OP-1250 caused findings in rats and dogs for the following study parameters: in-life phase (body weight, food consumption, clinical signs of toxicity), hematology (red and white blood cell populations, as well as platelets, with some concordant changes in bone marrow), coagulation (fibrinogen), serum clinical chemistry consistent with effects on liver and kidney, ophthalmology (detached retina), and anatomic changes in adrenal glands, liver, spleen, pituitary, thymus, lung, skeletal muscle, lymph nodes, skin, and gastrointestinal tissues, as well as changes in reproductive organs in males and females (ovary, vagina, uterus, mammary glands, prostate, seminal vesicles, testes, and epididymis). Between the rat and dog studies, there was generally good concordance of target organs specifically for changes in reproductive organs, hematological parameters, liver, adrenal glands, and spleen. Most drug-related findings had correlative effects between anatomic changes and monitorable peripheral changes (hematology, clinical chemistry). OP-1250-related effects to the retina were in the rat study only.

Most adverse findings in rats and dogs occurred at dose levels that also had adverse or noteworthy findings in the in-life data, specifically body weight, food consumption, or clinical signs (tremors). Therefore, the adverse anatomic findings had premonitory effects that were detected as general health assessments.

A key feature of OP-1250 is the long plasma half-life that resulted in persistent systemic exposure for the entire 28-day treatment-free recovery period. Since the animals were exposed to OP-1250 for the duration of the recovery phase, few of the toxicities fully reversed.

In the Good Laboratory Practice (GLP) toxicology studies, the highest non-severely toxic dose was 30 mg/kg in rats and 30 mg/kg in dogs after 28 daily oral doses. Since most of the effects of OP-1250 are pharmacologically related and can be monitored clinically, the initiation of clinical trials at pharmacologically relevant doses is expected to be safe. Only at the highest dose of OP-1250 tested, (100 mg/kg) were retinal abnormalities seen in a single species (rats). No retinal toxicities were seen in rats at the next lowest dose tested in them (30 mg/kg) and no retinal abnormalities were seen at any dose in beagle dogs. In this trial, the dose of OP-1250 expected to be efficacious is well below the comparable dose in which retinal changes were observed in rats. OP-1250 is an amphiphilic cationic drug and these retinal changes in the rat may be due to its chemical structure. Tamoxifen is also an

amphiphilic cationic molecule and retinal abnormalities have been reported with tamoxifen. Rat retinal pigment epithelium was packed with crystalline-like inclusions at high doses of tamoxifen exposure (Lüllmann 1981). The exact incidence of tamoxifen retinal changes in humans is not known, but over 2 years at 20 to 30 mg daily, 1.5% to 15% of patients, respectively, showed retinal changes and tamoxifen at standard doses is generally well tolerated (Al-Tweigeri 1996).

A comprehensive review of OP-1250 is contained in the Investigator's Brochure (IB) supplied by Olema Pharmaceuticals. The investigator should review this document prior to initiating this study.

6.3 Rationale for Starting Dose and Dose Escalation Schema

In the 28-day GLP IND-enabling toxicity studies, the STD_{10} (defined as the dose at which 10% of animals had severe toxicity) in rats was not defined for OP-1250 because the dose of 30 mg/kg daily was well tolerated and not severely toxic, while at the next higher dose of 100 mg/kg there was significant ocular toxicity, including retinal epithelial cell vacuolation and retinal detachment. Therefore, a rat reference dose of 30 mg/kg, with less toxicity than associated with an STD_{10}, was used in place of STD_{10}. This dose of 30 mg/kg daily corresponds to a human equivalent dose (HED) of 290 mg daily. The highest non-severely toxic dose (HNSTD) in dogs was 30 mg/kg daily (HED of 990 mg daily).

The dose of 30 mg/kg daily in the rat generated the lowest HED (290 mg daily) and it was used to calculate the maximum recommended starting dose (MRSD). One-tenth of the HED of 30 mg/kg daily dose in rats is approximately 30 mg daily and represents the MRSD for Phase I.

Given the advanced cancer patient population, the proposed starting dose for the Phase I trial was set at 30 mg daily. Importantly, the predicted human area under the curve (AUC) at the dose of 30 mg daily (~4000 ng*h/mL) is expected to be approximately equivalent to OP-1250 in mice given efficacious doses (~5 mg/kg daily) in various animals models (~2000 ng*h/mL), and thus provides a potential therapeutic benefit for patients with cancer, while remaining well below the AUC at a dose that did not elicit severe toxicity in rats (~40,000 ng*h/mL) and the HNSTD in dogs (6000 ng*h/mL).

Modeling of potential human drug exposure based on steady state drug levels in preclinical animal species, animal and human microsome, hepatocyte clearance, and plasma binding studies suggest a starting dose of 30 mg, taken by oral capsule would be likely to achieve C-average 50 ng/mL.

Olema's preliminary determination of the target drug exposure for postmenopausal women with HR-positive/HER2-negative tumors that have previously progressed on hormonal therapy and continues to be HR-positive and/or have mutant ESRα is average concentration of 100 ng/mL, and a maximum concentration (C_{max}) of 200 ng/mL. This determination is based on xenograft and cell culture observations. Based on these investigations we propose a target dose exposure range (TDE range) of C-average 100 to 200 ng/mL, a C_{max} of 200 to 400 ng/mL, and an effective AUC (eg, ~2000-4000 ng*h/mL).

Dose Levels:

Dose escalation for Phase I, Part A will be as per Section 8.8.1, Table 6. Dose escalation will follow a rolling 6 design (Skolnik 2008). The available safety and PK data will be reviewed, and intermediary dose levels may be tested. Dose escalation will not exceed 360 mg daily. See Section 8.8 for further dose level details. Intermediate dose levels will be tested based on the PK profiles and toxicity observed in the initial cohorts. Dosing continues until PD, unacceptable toxicity, or other reason for treatment discontinuation.

6.4 Target Population

The target population for this study will be women and men who have progressed following hormonal therapy for advanced breast cancer. Subjects may have received a prior CDK4/6 or PI3K inhibitor. Data demonstrate additional benefit in pre- or peri-menopausal women taking LHRH agonists for ovarian ablation in addition to hormonal agents (Cardoso 2018). Both premenopausal women and postmenopausal women will be eligible for this study; however, premenopausal and perimenopausal women must be willing to take an LHRH agonist.

6.5 Previous and Ongoing Clinical Studies

6.5.1 Previous Clinical Studies

No human studies have been conducted with OP-1250, thus there is no previous human experience with this drug.

6.5.2 Ongoing Clinical Studies

In addition to this ongoing study, which has completed the Phase IA dose escalation portion, there are other ongoing studies in patients with breast cancer to evaluate the combination of OP-1250 with CDK 4/6 inhibitors and PIK3CA inhibitors in dose escalation and expansion studies. Furthermore, OP-1250 is being evaluated in healthy volunteers.

6.6 Study Rationale

There are a number of different mechanisms implicated in the development of endocrine resistance. Loss of ER expression is one possible cause, with between 10% and 20% of initially ER positive patients converting to negative on relapse (Bedard 2008). Another potential mechanism is the development of endocrine receptor mutations. Growth factors, such as epidermal growth factor (EGFR), insulin/insulin-like growth factors (IGFs), and fibroblast growth factor receptor (FGFR), and their respective signaling pathways have also been studied as potential mechanisms of endocrine resistance (Clarke 2015). The PI3K/AKT/mTOR signaling pathway activation plays a major role in the development of endocrine resistance and is a target of many therapies designed to overcome resistance (Augereau 2017).

OP-1250 demonstrates anticancer activity in preclinical models of endocrine resistance including in tumors with activating mutations in estrogen receptor 1 (*ESR1*). The mechanism of action of OP-1250 of complete estrogen blockade and ER degradation are unique and may have an important role in metastatic breast cancer after progression on other hormonal therapies.

In this study we plan to assess potential mechanisms of endocrine resistance by evaluating

6.7 Summary of Overall Risks and Benefits

Although the clinical benefit of OP-1250 has not yet been established, modulation of the ER is a well validated target and forms the basis for standard of care treatment. Nonclinical data support the hypothesis that OP-1250 may be more efficacious than current, approved therapies. The intent of this study is to begin to understand the safety, PK, and preliminary evidence of activity. If appropriate, OP-1250 would be studied in Phase II and Phase III trials to demonstrate meaningful therapeutic benefit to patients.

Subjects will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Estrogen antagonists commonly have adverse effects consistent with estrogen depletion, most notably, hot flashes and vaginal dryness.

Most OP-1250-related findings in the preclinical toxicology studies were consistent with the pharmacological mechanism, antagonism of ER in tissues, as well as changes in reproductive organs in males and females (ovary, vagina, uterus, mammary glands, prostate, seminal vesicles, testes, and epididymis). Between the rat and dog studies, there was generally good concordance of target organs specifically for changes in reproductive organs, hematological parameters, liver, adrenal glands, and spleen. Most drug-related findings had correlative effects between anatomic changes and monitorable peripheral changes (hematology, clinical chemistry). OP-1250-related effects to the retina were observed in the rat study only.

Most adverse findings in rats and dogs occurred at dose levels that also had adverse or noteworthy findings in the in-life data, specifically body weight, food consumption, or clinical signs (tremors). Therefore, the adverse anatomic findings had premonitory effects that were detected as general health assessments.

A key feature of OP-1250 is the long plasma half-life that resulted in persistent systemic exposure for the entire 28-day treatment-free recovery period. Since the animals were exposed to OP-1250 for the duration of the recovery phase, few of the toxicities fully reversed.

In the GLP toxicology studies, the HNSTD was 30 mg/kg in rats and 30 mg/kg in dogs after 28 daily oral doses. Since most of the effects of OP-1250 in animal models are pharmacologically related, reflecting excessive pharmacology or findings secondary to excessive pharmacology, and can be monitored clinically, the initiation of clinical trials at

pharmacologically relevant doses is expected to be safe. Only at the highest dose of OP-1250 tested, (100 mg/kg), were retinal abnormalities seen in a single species (rats). No retinal toxicities were seen in rats at the next lowest dose tested in rats (30 mg/kg) and no retinal abnormalities were seen at any dose in beagle dogs. OP-1250 is an amphiphilic cationic drug, similar to tamoxifen, and these retinal changes in the rat may be due to its chemical structure. In this trial, dose of OP-1250 expected to be efficacious is well below the comparable dose in which retinal changes were observed in rats.

[redacted]

There have been 4 events of grade 4 neutropenia in the Phase Ia of the study. The protocol has been amended to add additional complete blood count assessments. In addition, grade 4 neutropenia and decreased neutrophils are considered adverse events special interest (AESI).

7 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and the respective endpoints for each part of the study are presented in Table 5.

Table 5 Study Objectives and Endpoints

Phase I (Part A [Dose Escalation] and Part B [Dose Expansion])	
Primary Objectives	**Primary Endpoints**
• To identify the MTD and/or RP2D of OP-1250 (Part A [Dose Escalation]).	• Incidence and nature of DLTs as defined Section 8.8.2. • MTD and/or RP2D of OP-1250 when used as a single agent.
• To confirm the RP2D of OP-1250 (Part B [Dose Expansion]).	• RP2D of OP-1250 when used as a single agent.
• To assess the safety and tolerability of OP-1250 (Parts A [Dose Escalation] and B [Dose Expansion]).	• Incidence, nature, and severity of TEAEs and SAEs according to NCI-CTCAE version 5.0.
• To assess the PK of OP-1250 (Parts A [Dose Escalation] and B [Dose Expansion]).	• Plasma levels of OP-1250 at pre-defined intervals to establish PK parameters (including: C_{max}, C_{min}, T_{max}, AUC, $t_{½}$, and OP-1250 trough concentration at steady state).
Secondary Objectives	**Secondary Endpoints**
• To estimate the ORR defined as the CR + PR rate of OP-1250.	• ORR by evaluation of tumor response assessments using RECIST 1.1 in subjects with measurable disease.
• To estimate the CBR (CR + PR + SD ≥ 24 weeks) of OP-1250.	• 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]

Exploratory Objectives	Exploratory Endpoints
[redacted]	[redacted]
Phase II	
Primary Objectives	**Primary Endpoints**
• To estimate the ORR of OP-1250 in subjects with HR-positive/HER2-negative metastatic or locally advanced breast cancer with no evidence of CNS metastases who have progressed following at least 1 hormonal therapy regimen in the metastatic or locally advanced setting.	• ORR by evaluation of tumor response assessments using RECIST 1.1 in subjects without evidence of CNS metastases who have measurable disease.
• To assess the safety and tolerability of OP-1250.	• Incidence, nature, and severity of TEAEs and SAEs according to NCI-CTCAE version 5.0.
• To assess the plasma PK of OP-1250.	• Plasma levels of OP-1250 at pre-defined intervals to establish PK parameters (includes C_{max}, C_{min}, T_{max}, AUC, $t_{½}$, and OP-1250 trough concentration at steady state).
Secondary Objectives	**Secondary Endpoints**
• To estimate the CBR of OP-1250 in subjects with HR-positive/HER2-negative metastatic or locally advanced breast cancer with no evidence of CNS metastases who have progressed after receiving at least 1 hormonal treatment regimen in the metastatic or locally advanced setting.	• 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]	[redacted]

Exploratory Objectives	Exploratory Endpoints
[redacted]	[redacted]

Abbreviations: AUC = area under the curve; C = Cycle; CBR = clinical benefit rate; C_{max} = maximum concentration; C_{min} = minimum concentration; [redacted] D = study day; DLT = dose-limiting toxicity; DoR = duration of response; EOT = end-of-treatment; [redacted]; ESR1 = estrogen receptor 1; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; iCBR = intracranial clinical benefit rate; MTD = maximum tolerated dose; *mut* = mutant; NCI-CTCAE = National Cancer Institute – Common Terminology for Adverse Events; ORR = overall response rate; PFS = progression-free survival; PIK3CA = phosphoinositide 3-kinase alpha catalytic subunit; PK = pharmacokinetic; PR = partial response; [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase II dose; SAE = serious adverse event; SD = stable disease; $t_{1/2}$ = half-life; TEAE = treatment-emergent adverse event; T_{max} = time to maximum concentration; *wt* = wild-type

See Appendix E for RECIST V1.1

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a Phase I dose escalation and dose expansion and Phase II monotherapy open-label, first-in-human study to determine the dose limiting toxicity (DLT), maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D), to characterize the safety and pharmacokinetic (PK) profile, and to estimate the preliminary antitumor activity of OP-1250 as a single agent in adult subjects with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative metastatic or locally advanced breast cancer. Treatment and study subject evaluation will be performed in 28-day cycles. This study comprises 2 Phases: Phase I (Part A [Dose Escalation] and Part B [Dose Expansion]) and Phase II. [redacted]

Phase I: Part A (Dose Escalation) and Part B (Dose Expansion): This portion of the study will evaluate the safety and PK of a range of doses of OP-1250 administered orally to subjects and determine the MTD and/or RP2D. Part A will employ a rolling 6 dose escalation study design, whereby cohorts of 3 to 6 subjects will be sequentially enrolled and monitored for DLTs during the first cycle of study treatment. Part B will enroll approximately 30 subjects in the expansion phase at the RP2D, or in the event 2 dose levels are being considered for the RP2D, then approximately 30 subjects will be enrolled in each of the 2 dose levels. Approximately 42 subjects will be enrolled in Part A (dose escalation), and up to approximately 60 subjects will be enrolled in Part B (dose expansion). Up to a total of approximately 102 subjects may be enrolled in the Phase I portion of the study.

Phase II: This portion of the study further explores the clinical activity, safety, and PK of OP-1250 at the RP2D and will estimate the preliminary anti-tumor efficacy. Up to 88 evaluable subjects will be enrolled over 3 cohorts in the Phase II: Cohort A will enroll 50 subjects with measurable disease without evidence of CNS metastases (subjects in the expansion at the RP2D will be included in this cohort), Cohort B will enroll approximately 15 subjects with non-measurable (evaluable) disease without evidence of CNS metastases; and Cohort C will enroll approximately 15 subjects with CNS metastases. To allow for subject replacement up to a total of approximately 88 subjects may be enrolled in the Phase II portion of the study.

[redacted]

8.2 Discussion of Study Design, Including Choice of Control Group

The proposed study design is standard for first in human oncology trials assessing safety and tolerability. Neither a placebo nor an active control will be included in this study.

8.3 Selection of Study Population

8.3.1 Inclusion Criteria

Individuals eligible to participate in either part of the Phase I Part A (Dose Escalation) or Part B (Dose Expansion) and the Phase II portion of the study must meet all of the following criteria:

1. Age ≥ 18 years, including males and females.
2. Subject is willing and able to participate and comply with all trial requirements and to provide signed and dated informed consent prior to initiation of any trial procedures.
3. Subject has histologically or cytologically confirmed locally advanced or metastatic breast cancer for which standard curative measures do not exist.
4. Tumor must be HR-positive and HER2-negative as determined in the most recently obtained archival tumor tissue sample from a metastatic site (unless de novo diagnosis or no metastatic biopsy undertaken) using locally accepted criteria by the local pathology report. HR positive is defined as ER+/PR+, ER+/PR-, ER-/PR+

[redacted].

6. The subject must have received at least 1 prior hormonal regimen for locally advanced or metastatic disease.
7. Subject must have received at least 6 months of a prior continuous endocrine therapy for locally advanced or metastatic breast cancer.
8. Subject has a life expectancy ≥ 6 months in the opinion of the investigator.
9. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.
10. Females of childbearing potential must be willing to adhere to highly-effective contraception during the study and for 90 days following the last study drug administration:
    a. Highly effective contraception methods must include one of the following:
        i. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation,

symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

ii. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

iii. Male partner sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject and the success of the vasectomy must be medically confirmed as per local practice.

iv. Placement of a nonhormonal intrauterine device (IUD).

b. Additionally, females of childbearing potential, must meet all the following criteria:

i. Not pregnant, as confirmed by a negative serum pregnancy test (β-human chorionic gonadotropin) before starting study treatment.

ii. Not breastfeeding.

c. A female subject is considered to be of childbearing potential unless she meets one of the following criteria:

i. Is aged ≥ 60 years.

ii. Has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

iii. Has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone levels).

iv. Is menopausal (amenorrhea ≥ 12 months) while off drugs that interfere with ovarian function.

11. Male subject must be willing to adhere to highly-effective contraception during the study and for 90 days following the last study drug administration. Highly-effective contraception methods must include one of the following criteria:

a. Successful vasectomy.

b. For subjects who have not had a successful vasectomy, and are partners of women of childbearing potential, their partners adhere to any one of the following.

i. Hormonal contraception + male subject's use of a condom with spermicide.

ii. IUD (hormonal or non-hormonal).

iii. Bilateral tubal ligation + male subject's use of a condom with spermicide.

iv. Depo Provera + male subject's use of a condom with spermicide.

12. Pre and peri-menopausal female subjects must be willing to take a LHRH agonist ≥ 2 weeks before the first study drug administration and for the duration of the study.

13. Subjects must have not taken proton pump inhibitors (PPI) for 7 days prior to first study drug administration and agree to avoid taking PPI therapy for at least the first 2 cycles of therapy.

14. Subjects must have a corrected QT interval (QTcF) < 470 msec for females and < 450 msec for males (as calculated by the Fridericia correction formula).

15. Subjects must not have received prior hormonal therapy (including fulvestrant), CDK4/6 inhibitors, alpelisib, everolimus, or poly-ADP ribose polymerase (PARP) inhibitors within 2 weeks prior to the first administration of study drug.

16. Subjects must not have received prior chemotherapy within 2 weeks or investigational therapy within 4 weeks prior to the first administration of study drug or within 5 half lives of either chemotherapy or investigational agent (whichever is earlier). Subjects must not have received antibody therapy within 4 weeks prior to first administration of study drug.

17. Prior radiotherapy must have been completed at least 2 weeks prior to start of Cycle 1 with recovery of any toxicities to ≤ Grade 1 (except for alopecia).

18. Subjects must have had at least 4 weeks from major surgery.

19. Subjects must have had any toxicities from prior therapy resolved or be ≤ Grade 1 as defined by NCI-CTCAE, v 5.0 at the time of starting study treatment with the exception of alopecia.

20. Subjects have the following laboratory values obtained ≤ 28 days prior to first dose (NOTE: if performed more than 3 days before the first study drug dose, then these laboratory tests need to be repeated within 3 days of C1D1 or pre-dose on C1D1 to ensure ongoing eligibility - with the exception of coagulation tests):

    a. Serum creatinine ≤ the upper limit of normal (ULN) or has an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) formula.

    b. Total bilirubin ≤ 1.5 × ULN unless prior history of Gilbert's syndrome.

    c. Aspartate transaminase and alanine transaminase ≤ 2.5 × ULN, or ≤ 5 × ULN if due to liver involvement by tumor.

    d. Hemoglobin ≥ 9.0 g/dL without requirement for red blood cell (RBC) transfusion within the last 4 weeks.

e. Platelets $\geq 100 \times 10^9$ cells/L.

f. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ cells/L (without the use of hematopoietic growth factors within the prior 3 weeks).

g. Prothrombin time (PT) and INR $\leq 1.5 \times$ ULN, activated partial thromboplastin time (PTT) $\leq 1.5 \times$ ULN. If on chronic anticoagulation, the INR must be in the therapeutic range.

Additionally, for individuals eligible to participate in Part A (Dose Escalation) of the Phase I portion of the study:

21. The subject must have received no more than 2 prior chemotherapy regimens for locally advanced or metastatic disease.
22. Subjects must have evaluable disease. Subjects with both measurable and non-measurable disease are eligible.

Additionally, for individuals eligible to participate in Part B (Dose Expansion) of the Phase I portion of the study and in the Phase II portion:

23. Subjects must have measurable disease by RECIST 1.1 criteria
24. The subject must have received no more than 1 prior chemotherapy regimen for locally advanced or metastatic disease.
25. The subject must have had at least 1 and no more than 4 prior hormonal-based therapies for locally advanced, recurrent, or metastatic disease.
26. Subjects with brain metastases are eligible for the study (Phase I Part A, Phase I Part B, and Phase II Cohort C) if they meet all the following criteria:
    a. The subject's brain metastases have been treated or do not require urgent local treatment at the time of study enrollment.
    b. The subject has been off dexamethasone or is on a stable dose of dexamethasone of ≤ 2 mg daily (or an alternate steroid dosed at a level equal to ≤ 2 mg daily) for at least 2 weeks prior to first study drug administration.

Phase II Cohort A (measurable disease without evidence of CNS metastases):

27. Subjects must have measurable disease by RECIST 1.1 criteria.
28. Subject must not have evidence of CNS metastases. (Imaging of the brain is NOT required if the subject does not have symptoms suggesting CNS disease.)

Phase II Cohort B (non-measurable [evaluable] disease without evidence of CNS metastases):

29. Subjects must have non-measurable and evaluable disease.
30. Subject must not have evidence of CNS metastases. (Imaging of the brain is NOT required if the subject does not have symptoms suggesting CNS disease).

Additionally, for individuals eligible to participate in the Phase II Cohort C (CNS cohort)

31. The subject must have received no more than 3 prior chemotherapy regimens for locally advanced or metastatic disease.
32. The subject must have had at least one prior hormone-based therapy for locally advanced, recurrent, or metastatic disease.
33. Subjects must have evaluable disease. (Subjects with either measurable or non-measurable disease are eligible.)

8.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in either the Phase I or Phase II part of the study:

1. Subjects with a prior or concurrent malignancy whose natural history or treatment may interfere with the safety or efficacy assessment of the investigational regimen as determined by the investigator.
2. Subjects with known impaired cardiac function or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, congestive heart failure (New York Heart Association Functional Classification Class 2B-4) and uncontrolled hypertension (defined as systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg on anti-hypertensive medications).
3. Subjects with myocardial infarction or unstable angina within 6 months prior to the first administration of study drug.
4. Subject with a history of cerebral vascular disease within 6 months prior to the first administration of study drug.
5. Subject has an active infection that requires antimicrobial therapy.
6. Subject has a history of leptomeningeal disease or spinal cord compression.
7. Subject has a history of allergic reactions attributed to compounds of similar chemical composition to OP-1250.
8. Subject has a history of a pulmonary embolism or deep venous thrombosis within the last 6 months or subject has an increased risk of thrombosis as determined by the investigator. (Subjects on chronic anticoagulation are allowed).
9. Medical history or ongoing gastrointestinal disorders that could affect absorption of OP-1250 (such as active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper GI surgery including gastric resection and including difficulties with swallowing capsules).
10. Subjects requiring therapy with strong CYP3A4 inhibitors and inducers.
11. Subjects requiring medications with known risk of QT interval prolongation or increased risk of Torsades de Pointes.
12. Subject has a known HIV infection.
13. Subject has a known clinically significant history of liver disease consistent with

Child-Pugh Class B or C, including active viral or other hepatitis (eg, hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis.

14. Subject has clinically significant co-morbidities, such as uncontrolled pulmonary disease, CNS metastases that require treatment or steroid doses of > 2 mg, active infection, psychiatric disease, or any other condition that could impact the ability of the subject to participate in this study or otherwise has the potential to confound the study results.

8.3.3 Removal of Subjects from Treatment or Assessment

Subjects may withdraw their consent to participate in this study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the EOT visit (Table 1) should be carried out.

Olema Pharmaceuticals must be notified of all subject withdrawals as soon as possible. Olema Pharmaceuticals also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation by an individual investigator or site for poor enrollment or noncompliance.

Reasons for which the investigator or Olema Pharmaceuticals may withdraw a subject from study treatment include, but are not limited to, the following:

- Subject experiences disease progression by RECIST criteria (see Appendix E) (elevation in tumor markers in the absence of increased tumor measurements or clear clinical deterioration is not categorized as disease progression).
- Subject experiences unacceptable toxicity, ie,:
  - Subject develops unacceptable toxicity that does not resolve within the parameters defined in Section 8.10, Table 8.
  - Subject experiences toxicity that is determined by the investigator to be no longer safe for the subject to continue therapy.
- Subject requests to withdraw from the study treatment.
- Subject requires or has taken medication prohibited by the protocol.
- Subject is unwilling or unable to comply with the study requirements.
- Subject was erroneously admitted into the study or does not meet entry criteria.
- Subject is lost to follow-up.
- Subject becomes pregnant.

If a subject does not return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after 2 attempts, a certified letter should be sent to the subject (or the subject's legally authorized representative,

if appropriate) requesting contact with the investigator. This information should be recorded in the study records.

Prior to enrollment into the study, the investigator or designee must explain to each subject, that the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and Institutional Review Board (IRB)/Ethics Committee (EC) in order to analyze and evaluate study results. It is the investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as Health Insurance Portability and Accountability Act (HIPAA) from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

8.4 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. This unique identifier will be on all case report form (CRF) pages. Subjects in Part A (Dose Escalation) of the Phase I portion who are not DLT evaluable (as defined in Section 8.8.2) may be replaced as appropriate. DLT evaluable is defined as a subject who experienced a DLT and/or received at least 75% of the originally assigned doses in the first cycle. Subjects who withdraw from study before receiving 75% of the planned doses in the first cycle of treatment for reasons other than a DLT unrelated to study drug toxicity will be considered to have inadequate data to support dose escalation decisions.

Subjects in Part B (Dose Expansion) of the Phase I portion and subjects in the Phase II portion will be replaced if they are not evaluable for response (ie, received less than 1 cycle of therapy and/or did not have a post-baseline tumor assessment).

8.5 Treatments

8.5.1 Treatments Administered

Subjects will receive OP-1250 as in this study. 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 or designee and the sponsor. Olema Pharmaceuticals and its designee will provide the study site with a supply of OP-1250 sufficient for the duration of the study.

8.5.2 Identity of Investigational Product

The investigational product (IP) OP-1250 is a small molecule being developed as a CERAN for the treatment of subjects with metastatic or locally advanced HR-positive/HER2-negative breast cancer.

8.5.2.1 Product Characteristics

OP-1250 capsules will be supplied in tamper resistant- high density polyethylene bottles containing 1 of the 2 dose strengths: 15 mg or 60 mg.

The pharmacist or study staff will supply the appropriate dose for each dose cohort using either one or more of the capsule strengths.

OP-1250 will be supplied as follows:

- OP-1250 capsules, 15 mg.
- OP-1250 capsules, 60 mg.

Please see Pharmacy manual for more details.

8.5.2.2 Storage and Labeling

At a minimum, each bottle label shipped to the sites will provide the following information: lot number, study identification, required storage conditions, directions for use, and region specific- caution statements (including "New Drug – Limited by United States federal law to investigational use" language).

OP-1250 accountability records will be maintained by the pharmacy or designated drug preparation area at the study site. Upon receipt of OP-1250 supplies, the pharmacist or designated drug handler will inventory OP-1250 (separately for each strength) and complete the designated section of the shipping form. The shipping/inventory form must be sent to Olema Pharmaceuticals or its designee, as instructed.

OP-1250 should be stored at controlled room temperature 15°C to 30°C (59°F to 86°F). All study supplies must be kept in a restricted access area.

A complete dispensing log must be maintained for all OP-1250 dispensed and all capsules of OP-1250 must be accounted for.

8.5.3 Directions for Administration

OP-1250 will be administered orally once daily at approximately the same time of the day on an empty stomach. Subjects should be fasting for 2 hours prior to taking OP-1250 and for 1 hour post OP-1250 administration. For the first 2 cycles of therapy, subjects should take OP-1250 in the morning to allow for PK assessments. After the pre-dose PK sample is collected on C3D1, subjects may take OP-1250 at a time of day of their choosing, but should take the drug at approximately the same time each day. Cycles are repeated every 28 days.

On days of in-clinic visits, OP-1250 will be administered to the subject by staff at the clinic (the subject should be counseled not to take their OP-1250 dose at home on the day of the clinic visit). On non-clinic visit days, subjects should be fasting for 2 hours prior to taking OP-1250 and for 1 hour post OP-1250 administration. OP-1250 capsules should be swallowed with water (approximately 8 ounces or 240 mL) without chewing or sucking the capsule.

[redacted]

OP-1250 capsules should not be opened or crushed. Direct contact with the powder in OP-1250 capsules with skin or mucous membranes should be avoided. If such contact occurs, the subject should wash the affected areas thoroughly with cold water and soap.

In cases where a subject misses his/her normal dosing time, the subject may still take the dose within 12 hours of the regular dosing time. Subjects should not take 2 consecutive daily doses within 12 hours of each other.

If the subject vomits after taking OP-1250, this should be documented in the subject's source document or dosing diary, OP-1250 should NOT be re-administered.

Sufficient capsules will be dispensed to the subject to permit at least 4 weeks of therapy, unless more frequent dispensing intervals are deemed necessary by the pharmacist or designated drug handler. Subjects will be provided with a paper diary to record daily dosing. Subjects should not take OP-1250 at home on the days of their in-clinic visits.

8.6 Method of Assigning Subjects to Treatment Groups

The enrollment and treatment assignment will be centrally managed by Olema Pharmaceuticals and its designee. In Phase I, Part A (Dose Escalation), when a treatment dose group is open for enrollment, sites will submit a Subject Enrollment Form along with specified subject eligibility source documents for potential subject to Olema Pharmaceuticals and its designee. Olema Pharmaceuticals and its designee will assign a subject number and dose group for each subject that is accepted into the study. Part B will enroll approximately 30 subjects in the expansion phase at the RP2D, or in the event 2 dose levels are being considered for the RP2D, then up to approximately 30 subjects will be enrolled in each of the 2 dose levels. Sites cannot enroll or start dosing the subject without receiving the assigned subject number and treatment cohort and/or dose group from Olema Pharmaceuticals or its designee. Up to 88 evaluable subjects will be enrolled over 3 cohorts in the Phase II: Cohort A will enroll 50 subjects with measurable disease without evidence of CNS metastases (subjects in the expansion at the RP2D will be included in this cohort), Cohort B will enroll approximately 15 subjects with non-measurable (evaluable) disease without evidence of CNS metastases; and Cohort C will enroll approximately 15 subjects with CNS metastases. To allow for subject replacement up to a total of approximately 88 subjects may be enrolled in the Phase II portion of the study.

8.7 Selection of Doses Used in the Study

The starting dose of OP-1250 for Phase I, Part A (Dose Escalation) is 30 mg once daily. The rationale for the starting dose is presented in Section 6.3.

8.7.1 Selection of Timing of Dose for Each Subject

The half-life of OP-1250 is commensurate with once daily administration in humans.

8.8 Phase I (Dose Escalation and Dose Expansion)

Part A (Dose Escalation) of the Phase I study is to determine the MTD and the RP2D of OP-1250 when given as a single agent orally once daily for 28 days (1 cycle) in subjects with HR-positive/HER2-negative metastatic or locally advanced breast cancer. Part B (Dose

Expansion) of the Phase I study is to further define the safety and tolerability of the RP2D identified in Part A (Dose Escalation).

8.8.1 Part A (Dose Escalation) Dose Levels and Dose Escalation Plan

8.8.1.1 Dose Levels

Dose level for the next cohort enrolled will be determined according to Table 6, provided no DLTs have been observed during Cycle 1.

The available safety and pharmacokinetic data will be reviewed, and intermediary dose levels may be tested. A maximum dose of 360 mg once a day will be evaluated.

Intermediate dose levels will be tested based on the PK profiles and toxicity observed in the initial cohorts. Dosing continues until PD, unacceptable toxicity, or other reason for treatment discontinuation.

Phase I, Part A (Dose Escalation) will be per the dosing table below. Dose escalation will follow a rolling 6 design (see Section 8.8.1.2).

Table 6: Phase I, Part A (Dose Escalation) - Dose Levels OP-1250

Dose Level* Cohort #	Increase from Prior Cohort	Dose Level (mg)
-1	Not applicable	15
1	Not applicable	30
2	100%	60
3	100%	120
4	75%	210
5	43%	300
6	20%	360

* Intermediate dose levels will be tested

8.8.1.2 Dose Escalation Plan

In Part A (Dose Escalation), cohorts of 3 to 6 subjects will be enrolled at each OP-1250 dose level and each subject will participate in only 1 cohort. Subjects at each dose level will be treated and observed for DLT through the end of the first cycle.

The following rolling 6 dose escalation rules noted below will be employed, considering DLTs observed in Cycle 1. Cohorts of 3 to 6 subjects will be treated at each dose level. In the rolling 6 design, up to 6 subjects may be concurrently enrolled at each dose level of the study. The decision to escalate to the next highest dose level are made by the investigators participating in the Phase I study and representatives of the sponsor at a cohort review meeting after at least 3 subjects have completed Cycle 1. Decisions as to whether to enroll a new subject onto the current, next highest, or next lowest dose level are made based on the number of DLTs and the review of AEs. Dose level assignment is based on the number of subjects currently enrolled in the cohort, the number of DLTs observed, the number of

subjects at risk for developing a DLT (ie, subjects enrolled but who were not yet evaluable for toxicity), and the available PK results. If 2 or more DLTs at a given dose level are observed, the dose level will be de-escalated. Intermediate dose levels will be tested. Intra-subject dose escalation is not permitted during Part A (Dose Escalation).

Table 7: Maximum Tolerated Dose Determination and Cohort Expansion

Number of Subjects with a DLT at a Given Dose Level	Escalation Decision Rule
0 of 3, 4, 5 or 6 subjects	Enter 3 to 6 subjects at the next dose level.
≥ 2 of 3, 4, 5, or 6 subjects	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to 3 additional subjects will be entered at the next lowest dose level for a total of 6 subjects to be treated at that dose.
1 of 3, 4, or 5 subjects	Enter up to a total of 6 subjects at this dose level. If 1 of 6 subjects in this group experienced a DLT, then enter 3 to 6 subjects at the next dose level.
≤ 1 of 6 subjects at highest dose level administered	**This is the MTD. The MTD is defined as the highest feasible dose tested in which fewer than 33% of subjects experienced DLT attributable to the study drug, when at least 6 subjects were treated at that dose and were assessable for toxicity.**

DLT = Dose-limiting toxicity; MTD = maximum tolerated dose

In Phase I (Part A [Dose Escalation]), all participating sites are required to send in DLT notification forms within 24 hours of learning of the event (details will be provided in Study Reference Manual). DLT(s) will immediately be communicated to all participating sites via emails and/or conference calls. Additionally, site teleconferences between the sponsor and all participating sites will be held during the Phase I part of the study to discuss any suspected AEs and/or DLTs (Part A [Dose Escalation] only) that have occurred in each cohort. The Safety Committee will include investigators participating in the study, the Medical Monitor, and the sponsor's Medical Director and will review study drug related- toxicities from the current cohort during the site teleconferences before escalating to the next dose level.

8.8.2 Definition of Dose Limiting Toxicity

A DLT is defined as the occurrence of any of the following TEAEs that occur despite optimal medical management, graded using NCI-CTCAE, v 5.0 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.
- AST or ALT > 3× the ULN and a total bilirubin > 2× the 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 > 8× ULN or AST or ALT > 5× ULN for ≥ 14 days.
- ALT or AST > 3× 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 the same subject leading to DLT will be considered a single DLT.

Subjects in Part A (Dose Escalation) who are not DLT evaluable may be replaced as appropriate. DLT evaluable is defined as experienced a DLT and/or received at least 75% of the originally assigned doses in the first cycle. Subjects receiving less than 75% of the planned dose in Cycle 1 without a DLT will be evaluated in the overall safety analysis, but not for the purposes of dose escalation.

8.8.3 Maximum Tolerated Dose

For purposes of defining the MTD and/or expansion phase recommended dose of OP-1250, subjects will be evaluated according to the actual starting dose of OP-1250 during the first treatment cycle. For most subjects, this will be the dose cohort to which they were assigned. Subjects who receive at least 75% (21 days) of the planned doses in Cycle 1 will be considered to have sufficient safety data/follow-up to support dose escalation. Subjects who withdraw from study before receiving 75% of the planned doses in the first cycle of treatment for reasons unrelated to study drug toxicity will be considered to have inadequate data to support dose escalation. In such cases, replacement subjects may be enrolled to receive the same starting dose of OP-1250 as the subjects who withdraw prematurely.

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

8.8.4 Recommended Phase II Dose

Following Phase 1a dose escalation of OP-1250 from 30 mg to 300 mg QD, a recommended phase 2 dose (RP2D) range was defined of 60 to 120 mg QD. Sixty patients are planned for Phase 1b enrollment, with 30 patients at each dose level (60 and 120 mg). At 60 mg and 120 mg, OP-1250 demonstrated high oral bioavailability and dose proportional exposure. At 120 mg, OP-1250 consistently exceeded the predicted efficacy plasma concentration thresholds from preclinical models. Safety data from 37 patients enrolled in Phase 1b indicated no clinically meaningful difference in the frequency of TEAEs between the 2 dose levels (60 mg,

120 mg) as the most common TEAEs (≥10%) were nausea (28%, 21%), vomiting (17%, 16%), fatigue (17%, 5%), and headache (11%, 11%), respectively. Most events were Grade 1 or 2, with the exception of two Grade 3 events at 60 mg (diarrhea and anemia). There were no dose reductions or discontinuations due to an AE. Based on safety and pharmacokinetic data from Study OP-1250-001,120 mg OP1250 QD has been selected as the RP2D.

Since the RP2D has been determined, active subjects enrolled on the Phase I part of the study may be treated at the RP2D with approval of the Medical Monitor if the investigator or designee considers this in the best interest of the subject.

8.8.5 Phase I Dose Expansion Part B

Once the RP2D is determined in Part A (Dose Escalation), an additional 30 subjects will be enrolled at that dose level to further define the safety and tolerability of the RP2D. If 2 dose levels are being considered for the RP2D, then up to approximately 30 subjects will be enrolled in each of the 2 dose levels.

8.9 Phase II

When the MTD/RP2D is determined for single agent OP-1250 from Part A (Dose Escalation) and Part B (Dose Expansion) in the Phase I portions of the study, then the Phase II portion will be initiated. This portion of the study further explores the clinical activity, safety, and pharmacology of OP-1250 at the RP2D and will estimate preliminary anti-tumor efficacy. Up to 80 evaluable subjects will be enrolled over 3 cohorts in the Phase II phase 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.
- [redacted]

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.

8.10 Dose Modification for Phase I and Phase II

All AEs should be assessed according to the NCI-CTCAE, v 5.0. In the event of multiple toxicities, dose delays and modifications should occur in accordance with the highest grade AEs observed.

Institutional guidelines should be followed in the event of hypersensitivity reaction.

Subjects who experience a DLT or any of the following AEs in Cycle 2 and beyond will have study drug treatment interrupted. Dose modification will be allowed as per Table 8. Modified dose levels are shown in Table 9.

Dose Modification Guidelines for Intermediate Doses are presented in Table 10. The first dose reduction will be approximately 20% to 30%, the second dose reduction is

approximately 40% to 50%, and the third dose reduction is approximately 70% to 80%. Dose reductions below 15 mg daily are not allowed.

Dose modifications will only be made for TEAEs that are not clearly due to disease progression or extraneous causes.

Table 8: Dose Modification or Treatment Delay for OP-1250-Related Treatment-Emergent Adverse Events

Worst toxicity NCI-CTCAE, v5.0[a] Grade (v5.0)	Recommended dose modifications for OP-1250
Blood	
Febrile Neutropenia Grade 3	• Hold OP-1250 until ANC is ≥ 1.0 × 10^9/L or baseline. If treatment delay is ≤ 14 days, restart at 1 dose level lower. • If treatment delay is > 14 days, discontinue treatment.
Febrile Neutropenia Grade 4	• Discontinue treatment.
Investigations	
Neutropenia (ANC/neutrophils decreased)	
Grade 3 (ANC< 1.0-0.5 × 10^9/L)	• Hold OP-1250 until ANC is ≥ 1.0 × 10^9/L or baseline. If treatment delay is ≤ 7 days, restart at same dose. • If treatment delay is > 7 but ≤ 21 days, restart 1 dose level lower. • If treatment delay is > 21 days, discontinue treatment.
Grade 4 (ANC < 0.5 × 10^9/L)	• Hold OP-1250 until ANC is ≥ 1.0 × 10^9/L or baseline. If treatment delay is ≤ 7 days, restart 1 dose level lower. • If treatment delay is > 7 days, discontinue treatment.
Thrombocytopenia (platelet count decreased)	
Grade 3 (Platelets < 25-50 × 10^9/L) without bleeding	• Hold OP-1250 until platelet count is ≥ 75 × 10^9/L. If treatment delay is ≤ 7 days, restart at same dose. • If treatment delay is > 7 but ≤ 21 days, restart 1 dose level lower. • If treatment delay is > 21 days, omit dose and discontinue treatment.
Grade 4 (Platelets < 25 × 10^9/L) or Grade 3 with bleeding	• Hold OP-1250 until platelet count is ≥ 75 × 10^9/L. If treatment delay is ≤ 7 days, restart 1 dose level lower. • If treatment delay is > 7 days, discontinue treatment.
Renal	
Serum creatinine	
Grade 3 (> 3.0 – 6.0 × ULN)	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline, then restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower. If findings recur, discontinue treatment.
Grade 4 (> 6.0 × ULN)	• Discontinue treatment.
Hepatic[b]	
Grade 3 bilirubin increase	• Hold OP-1250 until resolution to ≤ Grade 1 and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower. If findings

Worst toxicity NCI-CTCAE, v5.0[a] Grade (v5.0)	Recommended dose modifications for OP-1250
	recur, discontinue treatment.
ALT or AST > 3× with concurrent > 2× ULN (or baseline) direct or total bilirubin For subjects with hepatic metastases, AST or ALT > 8× ULN or AST or ALT > 5× ULN for ≥ 14 days	• Hold OP-1250 until resolution to ≤ Grade 1 and restart 1 dose level lower. • If findings recur, discontinue treatment.
Grade 4 AST or ALT	• Discontinue treatment.
ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	• Discontinue treatment.
Gastrointestinal Toxicity	
Grade ≥ 3 nausea and/or vomiting and/or Grade 3 diarrhea not resolving within 72 hours with optimal treatment	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Cardiac	
Grade 2 Sinus bradycardia	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Grade ≥ 3 Sinus bradycardia	• Discontinue treatment.
Grade 3 QTc prolongation	• Hold OP-1250; address any serum electrolyte abnormalities. • Upon resolution of QTcF to ≤ 500 msec, resume OP-1250 at 1 dose level lower. • If findings recur, discontinue treatment.
Grade 4 QTc prolongation	• Discontinue treatment.

Worst toxicity NCI-CTCAE, v5.0[a] Grade (v5.0)	Recommended dose modifications for OP-1250
Eye Toxicity	
Grade 2 without changes in visual acuity	• Hold OP-1250, contact Medical Monitor, and have ophthalmologist examination. If no concerning findings suggestive of drug effect and resolved to a ≤ Grade 1 restart at 1 dose level lower. • If it recurs, hold OP-1250 and contact Medical Monitor. If resolved to a ≤ Grade 1, restart at 2 dose levels lower than original dose. • If it recurs again, hold OP-1250 and contact Medical Monitor. If resolved to a ≤ Grade 1, restart at 3 dose levels lower than original dose.
Grade 2 with changes in visual acuity Grade 3 or 4	• Discontinue treatment.
Neurologic Toxicity	
Grade 2 Headache	• If AE occurs that is not relieved with supportive care for 7 days the investigator or designee can reduce 1 dose level. • If AE occurs that is not relieved with supportive care for 7 days the investigator or designee can reduce 1 additional dose level. • If AE occurs that is not relieved with supportive care for 7 days the investigator or designee can reduce 1 additional dose level.
Grade 3 Headache	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Grade 2 Dizziness	• If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level.
Grade 3 Dizziness	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Other neurologic toxicity	
Grade 2	• If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 dose level.

Worst toxicity NCI-CTCAE, v5.0[a] Grade (v5.0)	Recommended dose modifications for OP-1250
	• If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level.
Grade 3	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Grade 4	• Discontinue treatment.
Psychiatric Disorders	
Grade 2 Confusion	• If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level.
Grade 3 Confusion	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Grade 4 Confusion	• Discontinue treatment.
Other Psychiatric Toxicity	
Grade 2	• If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level.

Worst toxicity NCI-CTCAE, v5.0[a] Grade (v5.0)	Recommended dose modifications for OP-1250
Grade 3	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Grade 4	• Discontinue treatment.
Other Non-Hematologic Toxicity	
Grade 1-2	• If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level. • If AE occurs that is not well treated with supportive care for 7 days the investigator or designee can reduce 1 additional dose level.
Grade 3	• Hold OP-1250 until resolution to ≤ Grade 1 or baseline and restart 1 dose level lower • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 2 dose levels lower than original dose. • If findings recur on 1 dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at 3 dose levels lower than original dose. • If findings recur, discontinue treatment.
Grade 4	• Discontinue treatment.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; QTc = QT interval corrected for heart rate; ULN = upper limit of normal;

[a] Common Terminology Criteria for Adverse Events (NCI-CTCAE v 5.0)

[b] The hepatic dose modification guidelines should be followed for abnormal liver function tests as defined in the above table, if not definitively due to progressive disease in the view of the treating physician.

Table 9: Dose Level Modification Guideline for the Phase I, Part A Dose Escalation

	Starting Dose	One Dose Reduction	Two Dose Reductions
Dose Level 1	30 mg daily	15 mg daily	15 mg every other day
Dose Level 2	60 mg daily	30 mg daily	15 mg daily
Dose Level 3	120 mg daily	60 mg daily	30 mg daily
Dose Level 4	210 mg daily	120 mg daily	60 mg daily
Dose Level 5	300 mg daily	210 mg daily	120 mg daily
Dose Level 6	360 mg daily	300 mg daily	210 mg daily

Table 10: Dose Modification Guideline for Phase I, Part B Dose Expansion and Phase 2

Starting Dose (mg daily)	First Dose Reduction (mg daily)	Second Dose Reduction (mg daily)	Third Dose Reduction (mg daily)
120	90	75	45
90	75	60	30
75	60	45	30
60	45	30	15
45	30	15	not applicable
30	15	not applicable	not applicable
15	not applicable	not applicable	not applicable

8.11 Treatment Duration

In the absence of unacceptable OP-1250 treatment-related toxicity or disease progression, subjects may receive OP-1250 treatment for up to 1 year and beyond 1 year with the agreement of the investigator or designee and the sponsor.

Treatment will continue until any 1 of the following occurs:

- SAE or AE that requires dose discontinuation as described in Section 8.10, Table 8.
- Progressive disease as determined by RECIST 1.1 (see Appendix E) (Tumor marker elevations in the absence of unequivocal radiologic progression of target or non-target lesions is not considered disease progression. Per RECIST 1.1, disease progression requires an overall disease burden increase based on the change in non-measurable disease that is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume,' which is equivalent to a 20% increase in diameter in a measurable lesion.)
- Initiation of non-protocol anticancer therapy.
- Illness or condition that may interfere with the subject's participation or require treatment discontinuation.
- Treating investigator or designee's determination that continuation of protocol therapy is not in the subject's best interests.
- Pregnancy.
- Noncompliance.
- Voluntary withdrawal of consent.
- Sponsor termination of the study.

8.12 Blinding

This is an open-label study with no placebo or comparators.

8.13 Prior and Concomitant Medications

All prescription and over-the-counter medications, including vaccinations, taken by a subject within 30 days before the first study drug administration will be recorded in the designated electronic CRF (eCRF).

The following actions should be considered with the following medications/therapies:

- PPIs should be avoided and are prohibited during the first 2 cycles of therapy. After that, PPI may be used only if other methods of symptom control have been ineffective. The Medical Monitor should be notified if PPI are started. The use of H2 blockers is strongly discouraged. If the subject experiences symptoms of gastric acid reflux that are not relieved with conservative measures (small meals, no eating after 6 PM, avoiding foods that stimulate stomach acid such as caffeine, alcohol, tomatoes, spicy foods), the investigator or designee may prescribe H2 blockers to be taken once or twice a day provided they are taken at least 2 hours prior to (or post) the OP-1250 dose; however, 4 hours is preferred.
- No other cancer therapies or investigational agents are permitted during the entire duration of the study treatment.

Based on the in vitro drug-drug interaction profile of OP-1250, the types of concomitant medications to avoid or to use with caution are presented in Table 11.

Table 11: Types of Concomitant Medications to Avoid or Use with Caution

Concomitant Medication Types	OP-1250 Characteristic	Potential Effects of Co-Administration	Approach
Prolongs QT	Unknown	Possible increased risk of Torsades de Pointes	Avoid (see Appendix C)
Strong CYP3A4 Inhibitors or Inducers	Metabolized primarily by CYP3A4	OP-1250 levels may be increased if administered with CYP3A4 inhibitors or decreased with CYP3A4 inducers	Avoid (see Appendix B)
P-gp substrates and BCRP substrates	Potential inhibitor of intestinal P-gp	May increase drug levels of concomitant medications that are substrates for intestinal P-gp (eg, digoxin) and BCRP substrates (eg, sulfasalazine)	Use P-gp and BCRP substrates with narrow therapeutic index with caution (see Appendix D)
Substrates of CYP2C8 and CYP2C9	Potential time dependent inhibitor of CYP2C8 and CYP2C9	May increase drug levels of concomitant medications that are substrates for CYP2C8 (eg, repaglinide) or CYP2C9 (eg, [S]-warfarin)	Use CYP2C8 and CYP2C9 substrates with narrow therapeutic indexwith caution (see Appendix D)
PPIs and H2 Blockers	Absorption may be affected by gastric pH.	Co-administration may affect the absorption of OP-1250	**PPIs should be avoided and are prohibited during the first 2 cycles of therapy. The use of H2 blockers is strongly discouraged. (See the first bullet point of Section 8.13 for full details.)**

Abbreviations: CYP = cytochrome P450 isozyme; H2 = histamine 2 receptor; P-gp = P-glycoprotein; PPI = proton pump inhibitor

Although in vitro, OP-1250 appears to be a substrate, primarily, of CYP3A4 and as such its exposure may be increased by CYP3A4 inhibitors (eg, itraconazole) and reduced by CYP3A4 inducers (eg, rifampin), results from in vivo studies are not yet available. Therefore, subjects should avoid strong CYP34A inhibitors or inducers if possible. However, their use in this study is not exclusionary.

Pre- and perimenopausal women must take an LHRH agonist of physician's choice.

Medications for nausea, vomiting, diarrhea, and constipation may be given according to the standard of care guidelines at the discretion of the investigator or designee. Granisetron (or other) is preferred over ondansetron due to the potential prolongation of the QT interval with ondansetron.

Bisphosphonates or other bone modifying agents are allowed provided the subject has been on these agents for at least 4 weeks prior to Cycle 1.

Subjects who have febrile neutropenia (FN) should receive antibiotics per standard of care. G-CSF may be used at the investigator or designee's discretion.

Other medications considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded in the eCRF.

8.14 Treatment Compliance

The importance of treatment compliance should be emphasized to the subject. Subjects will be given take-home kits and detailed instructions on how to take medications at home. Subjects will be instructed to return all used and unused study drug containers at each study visit. Subject compliance with the dosing regimen will be assessed by reconciliation of the used and unused study drug at each clinic visit. The quantity dispensed, returned, used, lost, etc., must be recorded on the dispensing log provided for the study. Compliance will be monitored and documented by site personnel on the appropriate form. The site personnel will question the subject regarding adherence to the dosing regimen by reviewing dosing dates and times on the used bottles, recording the number of capsules and strengths returned, the date returned, and determining treatment compliance before dispensing new medication to the study subject.

8.15 Investigational Product Accountability

The investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP received, subjects to whom IP is dispensed (subject-by-subject dose specific accounting), and IP lost or accidentally or deliberately destroyed. Any unused capsules shall be returned and be reviewed by the site staff and sponsor's monitor before they are destroyed. The investigator or designee must retain all unused or expired study supplies until the Olema Pharmaceuticals designated monitor has confirmed the accountability data.

8.15.1 Return and Disposition of Clinical Supplies

Unused study drug must be kept in a secure location for accountability and reconciliation by Olema Pharmaceuticals designated monitor. The investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after Olema Pharmaceuticals or its designee has granted approval for drug destruction. The Olema Pharmaceuticals designated monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to Olema Pharmaceuticals or its designee and retained in the investigator's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to Olema Pharmaceuticals' designee upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by Olema Pharmaceutical's designee.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

8.16 Dietary or Other Protocol Restrictions

Subjects should be advised to avoid grapefruit/grapefruit juice, Seville orange/Seville orange juice, and St. John's wort due to the possibility of interactions of these substances with the pharmacokinetics of OP-1250.

[redacted]

8.17 Efficacy, Safety, and Additional Variables

The Schedule of Events in Table 1, Table 2, Table 3, and Table 4 describe the timing of required evaluations.

8.17.1 Efficacy Variables

Efficacy variables include overall response (CR and PR) as determined by the subject's best tumor response, clinical benefit rate, [redacted] Overall response (CR and PR) as determined by the subject's best tumor response, clinical benefit rate, [redacted] will be assessed using RECIST 1.1 (see Appendix E), which includes evaluation of both the CNS and non-CNS compartments. [redacted]

8.17.2 Safety Variables

Safety will be assessed by periodic physical examinations, 12-lead ECGs, clinical laboratory assessments, and monitoring of AEs. Additional clinical laboratory assessments and 12-lead ECGs will also be obtained when clinically indicated.

8.17.3 Additional Variables

[redacted]:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

9 DEFINITION OF AN ADVERSE EVENT

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution. An AE may include inter-current illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (eg, worsening of asthma). Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. In NCI-CTCAE, v 5.0, unequivocal neoplastic disease progression is captured as the verbatim term of disease progression under the System Organ Class "General". When an AE of disease progression meets the requirements to be considered serious, the verbatim term should be reported as disease progression and should not be reported as an SAE. Evidence that the AE or death was a manifestation of underlying disease (eg, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be documented in the EDC.

The reporting period for AEs is the period from administration of the first dose of study drug through 30 days after the last administration of study drug. All related AEs will be followed to resolution, stabilization, or loss of contact with the subject. All unrelated AEs will be followed until the time of the Safety Follow-up visit, which is between 30 to 42 days after the EOT visit

The investigator will assess AEs for severity, for relationship to IP, and whether the event meets 1 or more of the definitions of an SAE (see Section 9.1).

The investigator will determine the severity of each AE and will record it on the source documents and in the AE eCRF, using NCI-CTCAE, v 5.0.

The investigator will determine the relationship of an AE to the IP and will record it on the source documents and in the AE eCRF. All AEs should be considered related to the study drug unless such relationship can be definitely excluded.

In order to classify AEs and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered in the eCRF, using MedDRA.

9.1 Serious Adverse Events

A SAE is defined as any AE that:

- Results in death (ie, the AE actually causes or leads to death).
- Is life threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- Requires or prolongs in-patient hospitalization.
- Results in persistent or significant disability or incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Results in a congenital anomaly or birth defect in a neonate/infant born to a mother exposed to IP prior to conception or during pregnancy.

- Is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or require medical or surgical intervention to prevent 1 of the outcomes listed above).

The reporting period for SAEs is the period from administration of the first dose of study drug through 30 days after the last administration of study drug. SAEs reported to the investigator outside of this reporting period will be reported to Olema Pharmaceuticals or its designee if, in good medical judgment, the event has any bearing on the study data. SAEs must be followed by the investigator until resolution, or until the subject is lost to follow-up, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

Any SAE, whether or not considered related to study drug, will be reported immediately (within 24 hours of learning of the event) to Olema Pharmaceuticals or its designee using the electronic data capture system. If the electronic data system is unavailable, the SAE may be reported by fax using the study-specific SAE Report Form, but should be entered in the electronic data capture system as soon as it becomes available. In addition to the outcome of the SAE, any medication or other therapeutic measures used to treat the event will be recorded in the appropriate eCRF page(s). Investigators or designees should not wait to collect additional information that fully documents the event before notifying Olema Pharmaceuticals or its designee of an SAE. Olema Pharmaceuticals may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators or designees submit additional information requested by Olema Pharmaceuticals or its designee as soon as it becomes available.

Reporting of SAEs to the IRB/EC will be done in compliance with the standard operating procedures and policies of the IRB/EC and with applicable regulatory requirements. Adequate documentation must be obtained by Olema Pharmaceuticals or its designee showing that the IRB/EC was properly and promptly notified as required.

The SAE form should be faxed to [redacted]

The investigator is encouraged to discuss with the Medical Monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is as follows:

[redacted]

9.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) are required to be reported by the investigator to the sponsor within 24 hours after learning of the event regardless of the causality to study drug. The most appropriate diagnosis or if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the sponsor, either as an SAE or as an AESI.

AESI for OP-1250 are:

- Neutropenia Grade 4.
- Decreased neutrophils Grade 4.

9.3 Pregnancies

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the study or within 90 days following cessation of treatment or, if the subject initiates new anticancer therapy, 30 days following cessation of treatment, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Study Manual.

Please refer to the Study Manual for further details on the pregnancy reporting procedure and associated report form.

10 STUDY PROCEDURES, EVALUATIONS, AND SCHEDULE

10.1 Screening and Baseline Assessments

At the start of the screening period, prospective study subjects will be fully informed about the nature of the study and possible risks. Subjects must read and sign the informed consent form (ICF) after the investigator has answered all questions to the subject's satisfaction.

After obtaining informed consent, subjects will undergo screening procedures to confirm eligibility to participate in the study. Screening procedures must be performed within 28 days prior to initiating study therapy. The investigator must evaluate the subject's medical history and the results of all screening assessments to determine study eligibility before the subject is enrolled.

The following evaluations and procedures will be performed within 28 days prior to the first study drug administration (C1D1):

- Signed informed consent.
- Medical history, including demographics and prior cancer therapy (see Section 10.2.1).
- Complete physical examination (see Section 10.2.2); vital sign measurements, including height and weight (see Section 10.2.4); and ECOG PS (see Section 10.2.3).
- 12-lead ECG (see Section 10.2.5).
- Prior and concomitant medication and therapies (see Section 10.2.8).
- Laboratory assessments (hematology, chemistry, coagulation, fasting serum lipid profile, urinalysis, serum pregnancy testing[redacted]) (see Section 10.2.6). Hematology and chemistry tests will be done within 3 days prior to the C1D1 visit and results checked against eligibility criteria prior to dosing at Cycle 1. When noted as "CBC only," all hematology tests are to be performed.
- Pregnancy test (see Section 10.2.6.6)
- Radiological assessments (see Section 10.3.1).
- Tumor measurement (see Section 10.3.2).
- [redacted]

If the subject meets all inclusion/exclusion criteria after the Screening visit(s), the site will follow the procedures described in Section 8.6 for subject enrollment.

10.2 General Eligibility and Safety Assessments

10.2.1 Medical History and Demographics

The investigator or designee will obtain a detailed medical history, including previous cancer history, by interviewing the subject during Screening. The medical history should include types of treatment for adjuvant therapy and detailed history for the treatment of metastatic disease including types of therapy, dates and best response to therapy. Medical history should also include current and past illnesses and conditions; current symptoms of any active medical

condition; surgeries and procedures; allergies; and social history (eg, smoking, alcohol, illegal substances).

Demographic information, such as the subject's age, ethnicity, and race will be collected by interview with the subject at Screening.

10.2.2 Physical Examination

A complete physical examination will be performed at Screening and during the EOT visit. Symptom directed physical examination will be performed at every visit, with exception C1D2 where no physical examination is required or if there is a laboratory only visit.

10.2.3 ECOG Performance Status

The ECOG Performance Status will be assessed as described in Appendix A.

10.2.4 Vital Signs, Height, and Weight

Vital signs, including blood pressure, pulse rate, respiration rate, and temperature, and weight will be measured. Height will be measured at Screening (baseline) only.

10.2.5 Electrocardiogram

Triplicate ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. ECGs will be performed in triplicate with a 10-second rhythm strip. When time-matched with a PK sample collection, the ECG should be obtained first. ECGs should be obtained before the assessment of blood pressure and other vital signs.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine read corrected QT value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range. It is preferable that the ECG machine provided for the study is used as it has capacity to calculate the standard intervals automatically.

At each time point, subjects will have 3 consecutive 12-lead ECGs performed 2 to 5 minutes apart to determine mean QTc. If the mean QTcF is prolonged (>500 msec, ie, NCI-CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed and the Medical Monitor notified.

In addition, repeat ECGs should be performed hourly for at least 3 hours until the QTcF interval falls below 501 msec. If QTcF interval reverts to less than 501 msec, and in the judgment of the investigator or designee and sponsor is determined to be due to cause(s) other than IP, treatment may be continued with regular ECG monitoring. If, in that timeframe, the QTcF rises above 500 msec the IP will be held until the QTcF decreases to 500 msec. Subjects will then restart the IP at the next lowest dose level. If the QTcF has still not

decreased to 500 msec after 2 weeks, or if at any time a subject has a QTcF >515 msec or becomes symptomatic, the subject will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF is due to IP, thorough consideration should be given to potential precipitating factors (eg, change in subject clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

[redacted] In addition to the planned ECG schedule, an unscheduled ECG should be collected pre-dose as soon as possible after a SAE, and if OP-1250 is dose reduced, pre-dose at the next clinic visit (at least a week after the subject has taken OP-1250 at a reduced dose).

10.2.6 Clinical Laboratory Assessments

Any abnormal clinical laboratory test results determined to be clinically significant by the investigator should be repeated (at the investigator's discretion) until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the investigator determines that the abnormal value is no longer clinically significant.

All clinical laboratory result pages should be initialed and dated by an investigator, along with a comment regarding whether or not the result is clinically significant.

The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the investigator will be recorded in the AE eCRF.

AEs will be graded using NCI-CTCAE v 5.0 criteria.

10.2.6.1 Hematology

Hematology assessments include CBC with differential, platelets, and hemoglobin.

10.2.6.2 Serum Chemistry

Serum chemistry assessments will include blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, total protein, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, and glucose.

10.2.6.3 Fasting Lipid Profile

The fasting lipid profile will include total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.

10.2.6.4 Coagulation

The coagulation assessment will include INR and PTT.

10.2.6.5 Urinalysis

Urine samples will be collected and macroscopic assessment of the amount of protein, glucose, white blood cells, and red blood cells will be performed (levels should be recorded if available) and microscopic analysis will be performed if an abnormality is noted.

10.2.6.6 Pregnancy Testing

Serum pregnancy tests will be performed only in women of child-bearing potential. Either serum or urine pregnancy test will be performed within 3 days prior to C1D1 and every cycle thereafter and at the EOT visit.

[redacted]

10.2.7 Adverse Events

Adverse events will be recorded after administration of the first dose of study drug (AEs reported between signing the informed consent form and before C1D1 dose administration will be captured as medical history).

10.2.8 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a subject within 30 days before the first study drug administration will be recorded in the designated electronic CRF (eCRF). Any concomitant medications added or discontinued during the study should be recorded in the eCRF.

10.3 Procedures to Assess Efficacy (Biopsy and Disease Assessment)

10.3.1 Radiologic Assessments

Computed tomography (with contrast) or MRI of chest, abdomen, and pelvis must be obtained within 28 days prior to the first IP dose. The same method (CT with contrast or MRI) must be used throughout the study. Subjects with brain metastasis should have MRI scans of the brain.

Radiographic assessment (and physical assessments of malignancy) should be performed at every 2 cycles starting at C3 (ie, C5, C7, C9, etc). Assessments must be performed prior to commencing treatment for that cycle. Post C9 assessment, subjects who have been determined to have obtained a clinical benefit from OP-1250 may reduce frequency of assessments to every 3 cycles (ie, C12, C15, C18, etc.) prior to commencing treatment for that cycle.

[redacted]

10.3.2 Tumor Assessments

Tumor assessments will be performed on subjects who have not previously progressed in the study, unless completed within the previous 4 weeks. Overall response (CR and PR) as

determined by the subject's best tumor response, clinical benefit rate, [redacted] will be assessed using RECIST 1.1 (see Appendix E), which includes evaluation of both the CNS and non-CNS compartments. [redacted]

10.4 Other Tests or Procedures

10.4.1 Pharmacokinetics

The plasma concentrations for OP-1250 will be determined using a liquid chromatography tandem mass spectrometry method. The measured OP-1250 plasma concentrations will be used to determine the PK parameters, including AUC, C_{max}, C_{min}, T_{max}, and $t_{1/2}$. Comparisons across dose levels will be made to assess proportionality. In addition, comparison between single-dose and multi-dose PK parameters will be made for assessment of steady state drug accumulation. Metabolites of OP-1250 may also be determined and measured.

Blood samples for the determination of plasma OP-1250 concentrations will be collected [redacted] according to the PK sampling schedule for all subjects is presented in Table 1 and Table 2. All subjects will have multiple PK samples obtained on C1D1, C1D8, and C2D1. A 24-hour post-dose PK will be drawn just prior to OP-1250 dosing on C1D2. In addition, all subjects will have a pre-dose PK drawn on C1D15, C3D1, C5D1, C7D1, and C9D1. [redacted]

In addition to the scheduled samples, an unscheduled PK blood sample should be drawn pre-dose as soon as possible after a SAE and following a dose reduction of OP-1250. Following a dose reduction, the pre-dose sample will be collected at the next clinic visit that is least 1 week after the subject has taken OP-1250 at a reduced dose.

[redacted]

[redacted]

10.5 Study Schedule

10.5.1 Screening

The Screening visit will within 28 days before dosing on Cycle 1, Day 1. The assessments to be performed at Screening are detailed in the Schedule of Events in Table 1.

10.5.2 Treatment

The Treatment Period comprises 28-day dosing 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 and beyond 1 year with the agreement of the investigator or designee and the sponsor. The assessments to be performed at each visit during the cycles of the Treatment Period are detailed in the Schedule of Events in Table 1, Table 2, Table 3, and Table 4.

10.5.3 End of Treatment

The EOT visit should occur within 42 days after administration of the last dose of IP.

For any subject who has been withdrawn from the study (see Section 8.3.3), the tests and evaluations listed for the EOT visit should be performed, if possible. The assessments to be performed at the EOT visit are detailed in the Schedule of Events in Table 1.

10.5.4 Safety Follow-up

Safety follow-up should occur at 30 to 42 days after the EOT visit. All related AEs will be followed to resolution, stabilization, or loss of contact with the subject. All unrelated AEs will be followed until the time of the Safety Follow-up visit, which is between 30 to 42 days after the EOT visit. The assessments to be performed at the Safety Follow-up visit are detailed in the Schedule of Events in Table 1.

10.5.5 Schedule of Events

The assessments to be performed at each visit during the cycles of the Treatment Period are detailed in the Table 1 (Schedule of Events for All Subjects), Table 2 (Pharmacokinetic and

Electrocardiogram Sampling Schedule for All Subjects) [redacted]

10.5.6 Study Stopping Criteria

The study may be prematurely stopped due to the following reasons:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue the study.
- Any other reason as determined by the sponsor.

The Safety Committee will include investigators participating in the study, the Medical Monitor, and the sponsor's Medical Director and will meet periodically to review all safety and/or PK information in the expansion phase of the study.

11 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Data collected in this study will be displayed using summary tables, data listings, and graphs. Categorical data will be summarized using contingency tables (frequencies and percentages). For continuous data summary, statistics of mean, standard deviation, median, minimum, and maximum will be presented. Baseline is defined as the last assessment prior to the first dose of study drug.

11.1 Analysis Set

11.1.1 Enrolled Analysis Set

The enrolled analysis set includes all subjects who enrolled into the study after signing an ICF and satisfying inclusion/exclusion criteria.

11.1.2 Safety Population

The safety analysis set (SAF) will include all subjects who received at least 1 full or partial dose of OP-1250.

11.1.3 Dose-Limiting Toxicity Analysis Set

The DLT analysis set (DLTAS) will include all subjects in Part A (Dose Escalation) 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.

11.1.4 Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who received at least 1 dose of OP-1250 and have at least 1 valid post-baseline tumor assessment.

11.1.5 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.

11.1.6 Pharmacokinetic Analysis Set

The PK analysis set (PKAS) will include all subjects at who received least 1 dose of OP-1250 and have adequate post-baseline PK samples for PK parameters characterization.

11.2 Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, DLTs, laboratory values, electrocardiogram results, vital signs, and ECOG PS.

The safety data from Part A (Dose Escalation) will be summarized by dose cohort. The data from Part B (Dose Expansion) will be summarized overall and by *ESR1* mutation status. AEs will be classified by system organ class and PT using MedDRA with severities classified using the NCI-CTCAE, v 5.0 criteria.

All collected AE data will be listed. Separately, all SAEs will also be listed. All TEAEs regardless of attribution will be summarized by cohort, as follows:

- All DLTs (regardless of grade) – DLTAS.
- All AEs (regardless of grade or attribution).
- All Grade 3/4/5 AEs.
- All drug-related AEs (regardless of grade).
- All AEs leading to study drug or study discontinuation.
- All SAEs, including death.
- All AEs of special interest (regardless of grade).

A separate listing of on-study deaths (other than those related to PD) will be presented.

The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled protocol assessment time point. Changes will be calculated relative to the values collected at baseline. The incidence of Grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided. The toxicity grades for laboratory tests will be based on NCI-CTCAE, v 5.0 criteria. The use of blood transfusions (platelets, red blood cells) and/or growth factor support will be reported. Similar analyses will be done for selected chemistry tests (including liver and renal function tests). Subject listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in the subject listings and will include flags for high and low values.

Vital sign results (blood pressure, pulse, respirations, and temperature) will be summarized descriptively for each scheduled protocol time point. Changes will be calculated relative to the assessments at baseline.

Extent of exposure for study treatment including number of doses, total dose, dose duration, frequency of dose holding, dose reductions, and dose discontinuations, as well as treatment compliance (percent of actual to planned dosing) will be summarized by cohort.

11.2.1 Electrocardiogram Analyses

The analysis of ECG results will be based on subjects in the SAF with baseline and on treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate, QTc, using standard correction factors (ie, Fridericia's [default correction], Bazett's, and possibly a study specific factor, as appropriate). QTcF will be calculated using the Fridericia formula, as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Data will be summarized and listed for QT, heart rate, RR interval (RR), PR, QRS, QTc and by study arm and dose. Individual QT (all evaluated corrections) intervals will be listed by study arm time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval, and changes from baseline in corrected QT after treatment by study arm dose and time point. For each subject and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

[redacted]

Changes from baseline for the ECG parameters QT interval, heart rate, RR, QTc, PR interval, and QRS interval will be summarized by treatment and visit (time).

The number (percent of subjects with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Table 12: Safety QTc

	Borderline (msec)	**Prolonged (msec)**
Absolute Value	≥ 450 - < 480	≥ 480
Absolute Change	30 - <60	≥ 60

If more than 1 ECG is collected at a nominal time post-dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTc value ≥ 500 msec, but the mean of the triplicates is not ≥ 500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the ≥ 500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥ 500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also ≥ 500 msec. Changes from baseline will be defined as the change between QTc post-dose from the time-matched average baseline triplicates on Day 0, or the average of the pre-dose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of subject factors (covariates) on the relationship will be examined.

11.3 Efficacy Analysis

The efficacy and biomarker analyses will be conducted for the FAS and the EFS. [redacted] For Phase I, descriptive summaries will be presented by cohort.

Overall Response Rate:

Subjects with measurable disease who receive at least 1 cycle of OP-1250 and have a post treatment tumor assessment will be included in the determination of the ORR. [redacted] The estimate of the ORR will be accompanied by 2-sided 95% exact confidence intervals. The ORR will be determined using RECIST 1.1 (see Appendix E) for the entire body (which include both CNS and non-CNS disease) [redacted]

Subjects without measurable disease will not be included in the determination of ORR; however, they will be included in safety, secondary, and exploratory analyses where appropriate.

Clinical Benefit Rate

Clinical Benefit Rate (CR+PR+SD ≥ 24 weeks) and iCBR (intracranial CR + intracranial PR + subjects with intracranial SD for ≥ 24 weeks in the CNS) will be estimated and will be accompanied by 2-sided 95% exact confidence intervals.

[redacted]

11.3.1 Pharmacokinetic Analyses

Pharmacokinetic parameters will be determined for the PKAS using standard compartmental or non-compartmental methods. A listing of subjects excluded from the analysis set and individual data points excluded from the analysis will be provided. The final analysis of PK parameters will be calculated based on actual sample collection time, rather than scheduled times. For the purpose of dose escalation decisions, if actual sample collection times are not available from the database, the scheduled times may be used.

A listing of PK blood sample collection times as well as derived sampling times will be provided. OP-1250 concentrations will be summarized using appropriate descriptive statistics (eg, N, arithmetic mean, standard deviation, minimum, median, maximum, coefficient of variation [CV] %, geometric mean and CV associated to the geometric mean) for each cohort

per cycle and day. Concentrations that are below the limit of quantitation will be treated as zero for the computation of descriptive statistics and listed with the lower limit of quantitation indicated. Missing concentrations will be omitted from the calculation of descriptive statistics.

Plots of mean OP-1250 concentration-time data will be presented for each dose level per cycle. Individual OP-1250 subject concentration-time data for each cycle will be graphically presented on linear and semi-logarithmic scales.

PK parameters (non-exclusive) are described in Table 13:

Table 13: Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Observed maximum plasma concentration during a sample interval.
C_{min}	Minimum observed concentration during a sampling interval.
t_{max}	Observed time to maximum plasma concentration during a sampling interval.
t_{min}	Time of first minimum observed concentration.
λz	Elimination rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination (Cmax excluded).
$t_{½}$	Terminal elimination half-life, determined from the quotient 0.693/λz.
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable time point calculated by log-linear trapezoidal summation.
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity, calculated by log-linear trapezoidal summation and extrapolated to infinity by addition of the last observed quantifiable plasma concentration divided by the elimination rate constant λz (if %AUCext > 20%, $AUC_{0-\infty}$ will not be reported).
AUC_{ext}%	The percent of the area under the concentration-time curve which was extrapolated to infinity (%), calculated as (Clast/λz)/$AUC_{0-\infty}$ *100.
CL/F	Apparent clearance after oral administration, calculated from the quotient dose / $AUC_{0-\infty}$.
V/F	Apparent volume of distribution after oral administration.

In addition, the PK sparse exposure data from this study may be used in the development of population PK and PK/PD models. Pharmacokinetic plasma levels and parameters will be determined, listed, and summarized for the PKAS in the PK Analysis Plan (PKAP). Only samples with acceptable PK (as defined in the PKAP) will be included in the summary statistics and a listing of individual data points or subjects excluded from the analysis will be presented. Plasma concentrations will be listed by subject for the PK Population. Summary statistics of OP-1250 concentrations will be reported by dose level, Day and Cycle. Details of this analysis will be provided in the PKAP. Possible relationships between PK parameters, PD variables, safety, and efficacy may be examined.

11.4 Sample Size Determination

11.4.1 Phase I, Part A (Dose Escalation)

For Phase I, Part A (Dose Escalation), cohorts of 3 to 6 subjects will be enrolled in each OP-1250 dose group 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 42 subjects will participate in Phase I, Part A (Dose Escalation) to allow for 6 planned dose levels and intermediate dose levels.

At the end of Phase I, Part A (Dose Escalation), a comprehensive review of safety, tolerability, and pharmacokinetics data will be performed to assess whether 1 OP-1250 dose can be identified as the RP2D. In the event that this comprehensive review is equivocal for 2 doses of OP-1250 as the possible RP2D, then these 2 doses will be investigated in Phase I, Part B (Dose Expansion).

11.4.2 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 (Dose Escalation) as the RP2D, then approximately 30 subjects will be enrolled at this dose. If 2 doses of OP-1250 are advanced from Phase I, Part A (Dose Escalation), then each dose will enroll approximately 30 subjects, for a total of up to approximately 60 subjects.

Subjects not evaluable may be replaced in either Part A (Dose Escalation) or Part B (Dose Expansion); therefore, approximately 102 subjects may participate in Phase I, Parts A (Dose Escalation) and B (Dose Expansion).

At the end of Phase I, Part B (Dose Expansion), a comprehensive review of safety, tolerability, PK and preliminary anti-tumor activity data will be performed. If only 1 dose was advanced from Phase I, Part A (Dose Escalation), ie, 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 2 doses are advanced from Phase I, Part A (Dose Escalation), 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.

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 (eg, 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.

11.4.3 Phase II

The Phase II part of the study is designed to assess safety and to obtain a preliminary estimation of anti-tumor activity of OP-1250 in metastatic breast cancer subjects. A total of approximately 50 subjects with measurable disease who do not have CNS metastasis will be

treated at the RP2D. Subjects enrolled in the dose expansion (Phase I, Part B) at the RP2D will contribute to the estimation of anti-tumor activity. In addition, 2 exploratory cohorts will be enrolled consisting of approximately 15 subjects each: 1) subjects with non-measurable disease, and 2) subjects with CNS disease. Subjects not evaluable may be replaced; therefore, approximately 88 subjects will participate in the Phase II part of the study.

At the end of Phase II, a comprehensive review of the safety and preliminary anti-tumor activity data of all 50 subjects with measurable disease dosed at the RP2D will be performed to obtain a preliminary risk:benefit profile to guide further drug development of OP-1250. A sample size of 50 subjects will provide an estimation precision of ±15% for any binary event assessing safety (eg, any SAEs) or anti-tumor activity (eg, overall response, clinical benefit). This level of precision is regarded as clinically sufficient in the preliminary assessment of the risk:benefit profile to plan future clinical trials for OP-1250.

Subjects without measurable disease are being enrolled in the Phase II study 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]

Anti-tumor activity data of all 50 subjects dosed at RP2D will be examined [redacted]. The respective mutation status cohort may be expanded further if the comprehensive review of its safety and preliminary anti-tumor activity data indicates favorable risk:benefit ratio for these subjects with metastatic or locally advanced breast cancer for which standard curative measures do not exist.

11.5 Safety Monitoring and Early Stopping Guidelines

Safety will be monitored throughout the trial. Dose escalation will proceed according to the dose escalation scheme described in Section 8.8.1.2. If more than 1 subject has a DLT during the first cycle of treatment, dose escalation will stop. If any significant safety issues arise, the sponsor will be notified and if necessary, a decision to modify or terminate the trial (or 1 of the cohorts) will be made.

All participating sites are required to provide DLT notification forms within 24 hours of learning of the event. Additionally, site teleconferences between the sponsor and all participating sites will be held approximately every 1 to 2 weeks during the dose escalation phase to discuss any suspected AEs/DLTs that have occurred at each cohort.

Safety will be reviewed by the Safety Committee, comprising a participating investigator(s), the Medical Monitor, and the sponsor's Medical Director.

The overall responsibility of the Safety Committee is to protect the ethical, welfare, and safety interests of subjects recruited into the OP-1250-001 study and to facilitate decisions for escalation and expansion cohorts.

The Safety Committee will review and assess all available safety and efficacy data collected with specific focus on the risk:benefit of continuing specific cohort(s) during the interval

observation window. The Safety Committee will meet as required to determine escalation to the next cohort and at least quarterly during dose expansion to evaluate safety and efficacy data, to identify potential treatment harm and all-cause mortality/morbidity, and to act in an advisory capacity to the sponsor.

11.6 Changes in the Conduct of the Study or Planned Analyses

Protocol modifications, except those intended to reduce immediate risk to study subjects, may only be made by Olema Pharmaceuticals. The investigator or designee must submit all protocol modifications to the IRB/EC in accordance with local requirements.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by Olema Pharmaceuticals and the IRB/EC, and all active subjects must again provide informed consent.

12 ETHICS

12.1 Institutional Review Board or Ethics Committee

Prior to initiating the study, the investigator will obtain written confirmation that the IRB or EC is properly constituted and compliant with all US FDA requirements and local regulations. A copy of the confirmation from the IRB/EC will be provided to Olema Pharmaceuticals or its designee. The investigator will provide the IRB/EC with all appropriate material, including the protocol, IB, the ICF/Subject Informed Consent (PIC), and any other written information provided to the subjects, including all consent forms translated to a language other than the native language of the clinical site. The study will not be initiated until appropriate IRB/EC approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the investigator and copies are received at Olema Pharmaceuticals or its designee. The approval document should refer to the study by protocol title and Olema Pharmaceuticals, protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. Appropriate reports on the progress of the study should be made to the IRB/EC or Research Ethics Board, and Olema Pharmaceuticals or its designee, by the investigator in accordance with applicable governmental regulations and in agreement with policy established by the IRB/EC and Olema Pharmaceuticals.

12.2 Ethical Conduct of Study

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) according to ICH guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject, or his/her legally authorized representative will provide written, informed consent before any study-related tests or evaluations are performed.

12.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with the Declaration of Helsinki, ICH GCP and US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25 [a,b.], CFR 50.27, and CFR Part 56, Subpart A), HIPAA (for the US only), Organic Law 15/1999 of 13 December 1999 on the Protection of Personal Data (DPA) in Spain, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The investigator will prepare the ICF/PIC and HIPAA authorization/Data Protection Act (DPA) and provide the documents to Olema Pharmaceuticals or its designee for approval prior to submission to the IRB/EC. Olema Pharmaceuticals and the IRB/EC must approve the documents before they are implemented. If a subject is unable to sign the ICF/PIC and HIPAA authorization/DPA, a legal representative may sign for the subject. The investigator will provide copies of the signed ICF/PIC to each subject (or the subject's legal representative) and will maintain the original in the subject's record file.

13 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the investigator at each site must provide to Olema Pharmaceuticals or its designee a fully executed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of research subjects in this study.

The study will be administered by and monitored by employees or representatives of Olema Pharmaceuticals. Clinical research associates will monitor each site on a periodic basis and perform verification of source documentation for each subject as well as other required review processes. Olema Pharmaceutical's designee will be responsible for the timely reporting of SAEs to appropriate regulatory authorities as required.

14 CASE REPORT FORMS AND SOURCE DOCUMENTS

Authorized study site personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided. An eCRF is required and must be completed for each enrolled subject, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, study site charts, or other study-specific source documents). The investigator will ensure that the eCRFs are accurate, complete, legible, and completed in a timely manner following each subject's visit (unless required earlier for SAE reporting). The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed in the eCRFs are never obliterated or destroyed. As required by the protocol, eCRFs should also be completed for those subjects who fail to complete the study (even during the screening period). If a subject withdraws from the study, the reason must be noted in the eCRF and thorough efforts should be made to clearly document outcome.

The eCRFs for this study will exist within a web-based electronic data capture (EDC) system. After the investigator or the investigator's designees (eg, research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

The eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This signature serves to attest that the information contained in the eCRF is true.

15 STUDY MONITORING AND AUDITING

Qualified individuals designated by Olema Pharmaceuticals will monitor all aspects of the study according to GCP and standard operating procedures for compliance with applicable government regulations. The investigator agrees to allow these Olema Pharmaceuticals designated monitors direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records of the study subjects, and, if requested, agrees to assist the Olema Pharmaceuticals designated monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by Olema Pharmaceuticals or its designees.

Members of Olema Pharmaceuticals GCP Compliance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other regulatory agencies may also conduct an audit of the study. If informed of such an inspection, the investigator should notify Olema Pharmaceuticals immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

16 RETENTION OF RECORDS

The investigator must retain all study records required by Olema Pharmaceuticals and by the applicable regulations in a secure and safe facility. The investigator must notify Olema Pharmaceuticals of any change in the location, disposition, or custody of the study files. The investigator/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (eg, subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. No records relating to this study should be disposed of without the written approval of Olema Pharmaceuticals. It is the responsibility of Olema Pharmaceuticals to inform the investigator/institution as to when these documents no longer need to be retained.

17 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, national and local health authorities, Olema Pharmaceuticals, and the IRB for each study site, if appropriate.

18 PUBLICATION AND INFORMATION DISCLOSURE POLICY

All information provided by the sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of Olema Pharmaceuticals.

For clinical interventional studies in subjects, Olema Pharmaceuticals will post study results on websites such as https://clinicaltrials.gov/ and https://eudract.ema.europa.eu/ in accordance with FDA and EU reporting rules.

Any publication or presentation of the results of this study may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. Publication of scientific and clinical data will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE), the CONSORT (Consolidated Standards of Reporting Trials) group and Good Publication Practice (GPP).

19 STUDY DISCONTINUATION

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The investigator will be responsible for notifying the relevant study site's IRB/IEC. The sponsor will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the sponsor and the investigator or designee will assure that adequate consideration is given to the protection of the subjects' interests. As directed by the sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

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21 SIGNATURE PAGE

Protocol Title:
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 Number: OP-1250-001

Protocol Amendment 6: 28 June 2022

I have read the forgoing protocol and agree to conduct this study as in accordance with the current protocol.

Investigator Name	Signature	Date

Please return the form to Olema Pharmaceuticals or its designee. Contact details will be provided to the investigator. Please retain a copy for your study files.

22 APPENDICES

22.1 APPENDIX A: ECOG Performance Status Scale

Grade	Descriptions
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.

22.2 APPENDIX B: Examples of Strong CYP3A Inducers and Inhibitors to be Avoided

Strong CYP3A4 Inducers	Strong CYP3A4 Inhibitors
Apalutamide	VIEKIRA PAK2 (Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir)
Avasimibe	Boceprevir
Carbamazepine	Ceritinib
Enzalutamide	Clarithromycin
Ivosidenib	Cobicistat (Gs-9350)
Lumacaftor	Conivaptan
Mitotane	Danoprevir / Ritonavir
Phenytoin	Elvitegravir / Ritonavir
Rifampin	Grapefruit/ Grapefruit Juice
Rifapentine	Idelalisib
St John's Wort Extract	Indinavir
	Indinavir / Ritonavir
	Itraconazole
	Josamycin
	Ketoconazole
	LCL161
	Lonafarnib
	Lopinavir / Ritonavir
	Mibefradil
	Mifepristone
	Nefazodone
	Nelfinavir
	Posaconazole
	Ribociclib
	Ritonavir
	Saquinavir
	Saquinavir / Ritonavir
	Seville orange/ Seville orange juice
	Telaprevir
	Telithromycin
	Tipranavir / Ritonavir
	Troleandomycin
	Tucatinib
	Voriconazole

22.3 APPENDIX C: Example of Concomitant Medications with Known Risk of QT Interval Prolongation or Increased Risk of Torsades de Pointes to be Avoided

Concomitant Medications to Avoid
Disopyramide
Dofetilide
Domperidone (Non Us)
Donepezil
Dronedarone
Levosulpiride (Non Us)
Mesoridazine (Off Us Market)
Methadone
Moxifloxacin
Ondansetron
Oxaliplatin
Terodiline (Non Us)
Thioridazine
Vandetanib

22.4 APPENDIX D: Example of Concomitant Medication to be Used with Caution

CYP2C9 sensitive substrates	CYP2C8 sensitive substrates	P-gp sensitive substrates	**BCRP**
(S)-warfarin Tolbutamide	Daprodustat Dasabuvir Repaglinide	Digoxin Dabigatran etexilate Betrixaban Edoxaban Fexofenadine (terfenadine carboxylate) Talinolol	Rosuvastatin Sulfasalazine

22.5 APPENDIX E: RECIST V1.1

Disease response in target and non-target lesions will be assessed by the Investigator using RECIST v1.1 (https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf), according to the categories and criteria described in Table 14. The best overall response for each subject will be reported as the best response documented over the sequence of objective statuses recorded using the categories and criteria in Table 15.

When possible, the same qualified physician will interpret results to reduce variability.

Table 14: Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1) Guidelines for Tumor Response

Disease Response Criteria for Target and Nontarget Lesions	
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 LD.
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.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded (nadir) since the treatment started or the appearance of one or more new lesions.
Evaluation of Nontarget lesions	
Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level.
Non-CR/non-PD:	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
Key: LD = longest diameter.

Table 15: Overall Response Criteria

Subjects with Target and Nontarget Lesions			
Target Lesions	**Non-Target 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 evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
Subjects with Nontarget Lesions Only			
Non-Target Lesions	**New Lesions**		**Overall Response**
CR	No		CR
Non-CR / Non-PD	No		Non-CR / Non-PD
Not all evaluated	No		NE
Unequivocal PD	Yes or No		PD
Any	Yes		PD

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Key: CR = complete response; NE = inevaluable; PD = progressive disease.

Any subject with a CR or PR is to have repeat assessments performed at 4 weeks later to confirm the response.