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An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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16.1. Study Information

16.1.1. Protocol and Amendments

Protocol

An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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for
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A wholly owned subsidiary of Eli Lilly and Company
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by
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STUDY IDENTIFICATION

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PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

SPONSOR: Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
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SYNOPSIS

Title of study: An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Objectives:

The objectives of this study are:

Primary:

- To assess the effect of multiple doses of an H2 antagonist (ranitidine) administered with a single dose of LOXO-292 on the pharmacokinetics (PK) of LOXO-292 under fasted conditions in healthy adult subjects.
- To assess the effect of multiple doses of a proton pump inhibitor (PPI) (omeprazole) administered with a single dose of LOXO-292 on the PK of LOXO-292 given with a low-fat meal in healthy adult subjects.

Secondary:

- To determine the safety and tolerability of a single dose of LOXO-292 under fasted conditions alone, in combination with an H2 antagonist (ranitidine) under fasted conditions, and in combination with a PPI (omeprazole) given with a low-fat meal in healthy adult subjects.

Study design:

This is an open label, 3-period, fixed sequence study.

In Period 1, a single oral dose of LOXO-292 will be administered under fasted conditions. On Day 1 of Period 1, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 1.

In Period 2, multiple oral doses of ranitidine will be administered twice daily from Day 8 until Day 18 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 12 under fasted conditions. On Day 12, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. On Day 12, ranitidine will be administered 2 hours (± 10 minutes) after the LOXO-292 dose. On Days 8 - 11 and 13 - 18, the morning dose of ranitidine will be administered (with breakfast) approximately 2 hours (± 1 hour) after the planned or actual time of the Day 12 LOXO-292 dose and the evening dose of ranitidine will be administered (with a light meal/snack) approximately 10 hours (± 1 hour) prior to the planned or actual time of the Day 12 LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 12.

In Period 3, multiple oral doses of omeprazole will be administered once daily from Day 19 until Day 29 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 23 with a low-fat meal. On Day 23, omeprazole and a single oral dose of 160 mg of LOXO-292 will be coadministered within 30 minutes of the start of a low-fat meal, which will be entirely consumed within 30 minutes. On Days 19 - 22 and 24 - 29, omeprazole will be administered following a fast of 2 hours prior to and 1 hour after the omeprazole dose (Note: omeprazole will be administered at approximately the actual time of the Day 12 LOXO-292 dosing). Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 23.

There will be a washout period of 7 days between the LOXO-292 dose in Period 1 and the first dose of ranitidine in Period 2 and between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 30 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. A follow-up phone call will occur for all subjects who received at least 1 dose of study drug (including subjects who are terminated study early) 7 days (± 2 days) after EOT or ET.

In this study, physical examinations (PEs), 12-lead electrocardiograms (ECGs), vital signs, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) and concomitant medication recording will be performed at Screening and at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 4). Adverse events (AEs) and serious adverse events (SAEs) will be collected beginning at informed consent. AEs will be reported throughout the study (ie, from signing of the Informed Consent Form [ICF] until End of Study [EOS], or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

Study Completion is defined as the time of the last subject's follow-up phone call.

Number of subjects:
Twenty healthy, adult, male and female subjects (women of nonchildbearing potential only) are considered sufficient to assess the effect of multiple doses of an H2 antagonist (under fasted conditions) or a PPI (given with a low-fat meal) on the PK of LOXO-292.

Every attempt will be made to enroll at least 3 subjects of each sex in the study.

Subjects who withdraw or drop out of the study may be replaced if deemed necessary by the Sponsor.

Diagnosis and main criteria for inclusion:
Male subjects and female subjects of nonchildbearing potential, between 18 and 55 years of age, inclusive, at Screening, and within body mass index (BMI) range 18.5 to 32.0 kg/m^2, inclusive. Subjects will be in good general health, based on medical history, PE findings, vital signs, ECG, and clinical laboratory tests at Screening and Check-in (Day -1), as determined by the Investigator (or designee).

Investigational products, dose, and mode of administration:
LOXO-292 will be supplied by Loxo Oncology as 80 mg capsules for oral administration. Ranitidine will be supplied by Covance as 150 mg tablets for oral administration. Omeprazole will be supplied by Covance as 40 mg capsules for oral administration

Period 1: Subjects will be administered 160 mg LOXO-292 (2 x 80 mg capsules) on Day 1 administered under fasted conditions.

Period 2: Subjects will be administered 150 mg of rantidine twice daily from Day 8 of through Day 18, inclusive, administered with 160 mg LOXO-292 on Day 12 under fasted conditions.

Period 3: Subjects will be administered 40 mg of omeprazole once daily from Day 19 through Day 29, inclusive, administered with 160 mg LOXO-292 on Day 23 with a low-fat meal.

Duration of subject participation in the study:
Planned Enrollment/Screening Duration: up to 28 days (Day -29 to Day -2).

Length of Confinement: a total of 31 days (30 nights), from the time of Check-in (Day -1) through the 168-hour PK blood draw and end of study assessments (Day 30).

Follow-up Phone Call: 7 days (± 2 days) after EOT or ET.

Planned Study Conduct Duration: approximately 60 days

Criteria for evaluation:
Pharmacokinetics:
Serial PK blood samples for the analysis of plasma LOXO-292 concentrations will be collected from predose through 168 hours postdose.

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-292 (as appropriate): area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t}), area under the concentration time curve extrapolated to infinity ($AUC_{0-\infty}$), extrapolation for area under the concentration time curve ($\%AUC_{extrap}$), maximum plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), elimination rate constant (λZ), apparent systemic clearance (CL/F), and apparent terminal elimination half-life ($t_{½}$).

An analysis of variance (ANOVA) will be performed on the natural log (ln)transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}, using the appropriate statistical procedure.

Safety:
Safety will be monitored through 12-lead ECGs, PEs, concomitant medications, vital sign measurements, clinical laboratory tests, and AEs.

CCI [redacted]

Statistical methods:

Pharmacokinetics:

The primary analysis planned for this study is an analysis of variance (ANOVA) model that includes treatment as a fixed-effect and subject as a random-effect. CCI [redacted]

Safety:

All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory results, PE results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last nonmissing measurement before administration of LOXO-292 in each period. No formal statistical analyses are planned for the safety data.

More details on the analyses will be included in the Statistical Analysis Plan (SAP).

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATU	temporary authorization use
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
AV	atrioventricular
BMI	body mass index
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL/F	apparent systemic clearance
C_{max}	maximum observed concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
HCV	hepatitis C virus
HDYF?	How do you feel?
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
IC_{50}	50% inhibitory concentration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intrauterine device
λ_Z	apparent terminal elimination rate constant
LFT	liver function test
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve
PK	pharmacokinetic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell
RET	rearranged during transfection
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SPP	single-patient protocols
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time to maximum observed concentration
UA	urinalysis

Abbreviation	Definition
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

Refer to the current Investigator's Brochure (IB)[1] for detailed information concerning the pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product.

1.1. Background

LOXO-292 is a small molecule and selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase designed to competitively block the adenosine triphosphate binding site of the kinase. LOXO-292 was at least 250-fold more selective for RET than for 98% of 329 other kinases tested in a large *in vitro* screen. Consistent with such a high degree of selectivity, LOXO-292 caused significant cytotoxicity in human cancer cell lines that harbored endogenous, clinically relevant RET gene alterations but was much less cytotoxic against human cancer cell lines without RET alterations. Potent and selective inhibition of RET may provide clinical benefit to subjects with malignancies due to oncogenic alterations in RET or with other mechanisms of increased RET activity.

1.2. Summary of Nonclinical Studies

Cardiac safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) *in vitro* assay for human ether-a-go-go related gene (hERG) activity, in a GLP *in vivo* study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with electrocardiogram [ECG] monitoring) in minipigs. LOXO-292 had a 50% inhibitory concentration (IC_{50}) value of 1.1 μM in the GLP hERG assay, which is approximately 14- and 6-fold higher than the predicted maximum unbound concentration at the dose of 80 mg and 160 mg respectively twice daily. There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28 day-repeat dose- toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias. In the 3-month repeated-dose study, an increase in QTc interval was noted in female minipigs administered 5 mg/kg/day of LOXO-292, but the degree of the increase was small (approximately 7 to 12%). These low magnitude QTc changes were potentially LOXO-292-related but were not considered adverse.

Administration of LOXO-292 at single doses up to 45 mg/kg in male rats had no effect on respiratory function.

Potential effects of LOXO-292 on the central nervous system were evaluated as part of the GLP 28 day repeat-dose study in rats, in functional observational battery tests and locomotor activity assessments. Findings were limited to animals receiving the high dose on Week 4 of the dosing phase and were attributed to poor general body condition and weight changes associated with LOXO-292 administration rather than specific neurological effects. Additionally, no microscopic abnormalities in neuronal tissues were found.

In toxicology studies of LOXO-292 that were conducted in the rat and minipig, the primary pathologic findings for both species were in the tongue, pancreas, bone marrow, lymphoid tissues, physeal cartilage, and testes; while the gastrointestinal tract and ovaries were target tissues in minipig. Other target tissues identified in the rat included: multi-tissue mineralization, incisor teeth, lung, Brunner's gland, vagina, and possibly liver. Assessment of doses associated with moribundity/death revealed a steep dose response curve for both species. LOXO-292 was not mutagenic in the GLP bacterial mutation assay and was not clastogenic in the *in vivo* micronucleus assay. LOXO-292 was not found to be phototoxic when evaluated in an *in vitro* neutral red uptake phototoxicity assay. LOXO-292 is a developmental toxicant and is embryolethal.

In repeated dose toxicity studies in Sprague-Dawley Rats, minor changes suggestive of hepatic effects were higher alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels in males (≥ 20 mg/kg/day) and females (≥ 50 mg/kg/day), higher aspartate aminotransferase (AST) levels in those receiving the high-dose (both sexes), and a higher cholesterol concentration in males (≥ 20 mg/kg/day). Reversible, LOXO-292-related decreases in liver and thymus weights occurred in males at 75 and 45 mg/kg/day, respectively. None of these minor changes were correlated to any liver findings microscopically, suggesting minor functional alterations of the liver rather than overt hepatocellular injury. ALP levels were also increased in Göttingen minipigs administered 5 or 12 mg/kg/day in repeated dose toxicity studies; however, this change had no associated clinical or microscopic findings and was considered not adverse.

Based on preclinical pharmacology experiments with human cancer cells *in vitro* and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dosing regimens ≥ 40 mg/day.

Based on the nonclinical profile, including results from animal toxicology studies, theoretical risks of human exposure to LOXO-292 include the following: loss of appetite, decrease in body weight, increase in total white blood cells, neutrophils, and monocytes, decrease in albumin, increase in globulin, decreased albumin:globulin ratio, decrease in total protein, increased body temperature, lethargy, increase in cholesterol and triglycerides, increase in phosphorus, changes in taste sensation and/or development of xerostomia, gastrointestinal symptoms/signs: nausea, vomiting, loose stools, abdominal discomfort, decreases in red cell mass (red blood cell, hemoglobin, hematocrit) and reticulocytes, decrease in platelets, increases in liver function tests (LFTs; ALP, AST, and ALT), possible pancreas injury, possible QTc prolongation, possible decreased testicular weight, possible increased vaginal mucous and altered menstruation/ovulation

Refer to the current IB[1] for detailed background information on LOXO-292.

1.3. Summary of Clinical Studies

LOXO-292 is currently being studied in an ongoing global Phase 1/2 first in human Study LOXO-RET-17001 in patients with advanced solid tumors including RET fusion-positive non-small cell lung cancer, RET-mutant medullary thyroid cancer, and other tumors with increased RET activity. The starting dose of LOXO-292 was 20 mg once daily.

Single doses of 320 mg, 640 mg, and 720 mg have been administered to healthy volunteers in the ongoing Study LOXO-RET-18057. Interim safety and tolerability analysis showed that all dose levels were well-tolerated and there were no Grade ≥ 3 toxicities up to the maximum dose level tested (720 mg).

As of a March 30, 2019 data cut-off date, safety data was available from 422 patients with 240 mg twice daily as the highest dose administered.

During dose escalation, 2 dose-limiting toxicities (DLTs) were reported, both at the 240 mg twice daily dose level: 1 DLT of Grade 3 tumor lysis syndrome and 1 DLT of Grade 3 thrombocytopenia. The remaining 4 patients treated at this dose level cleared the 28-day DLT window and continued on study. The dosage of 160 mg twice daily was selected as the recommended Phase 2 dose (RP2D) based on safety data (N = 82) and preliminary efficacy data (N = 64 evaluable) for patients treated at doses from 20 mg once daily through 240 mg twice daily.[2,3,4]

Across 9 dose levels ranging from 20 mg once daily to 240 mg twice daily in these 422 patients, treatment-emergent adverse events (TEAEs) occurring in ≥ 15% patients were: dry mouth (30.8% total; 25.1% related), diarrhea (27.7% total; 12.8% related), hypertension (27.3% total; 16.8% related), fatigue (22.3% total; 14.5% related), constipation (21.8% total; 10.0% related), AST increased (21.6% total; 15.6% related), ALT increased (20.4% total; 15.4% related), headache (18.7% total; 6.9% related), nausea (18.0% total; 6.6% related), edema peripheral (17.3% total; 9.5% related), and blood creatinine increased (14.9% total; 7.3% related).

A total of 205 (48.6%) patients across all dose levels experienced ≥ Grade 3 TEAEs. TEAEs of ≥ Grade 3 that were considered to be related to study drug were reported in 95 (22.5%) patients across all dose levels. The most common Grade ≥ 3 TEAEs included hypertension (12.3%; 7.1% related), ALT increased (6.2%; 4.7% related), AST increased (4.7%; 3.1% related), hyponatremia (4.3%; 0.2% related), ECG QT prolonged (2.8%; 2.1% related), dyspnea and lymphopenia (each 2.6%; 0% and 0.9% related, respectively), diarrhea and thrombocytopenia (each 2.1%; 0.7% and 1.7% related, respectively). All other Grade ≥ 3 TEAEs occurred in less than 2% of patients overall.

Sixteen patients have died within 28 days of the last dose of study drug, and no deaths have been attributed to study drug.

As of April 15, 2019, pharmacokinetic (PK) data were available from 335 patients. LOXO-292 is absorbed after oral administration with a median time to maximum observed concentration (t_{max}) of approximately 2 hours.

As of March 30, 2019, Loxo Oncology initiated 40 single-patient protocols (SPPs), Special Access Scheme, Compassionate Use, or Temporary Authorization Use (ATU) cases to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing clinical study. For the SPPs, Special Access Scheme, Compassionate Use, or ATU cases, only serious adverse events (SAEs) are required to be reported. To date, there have been 39 SAEs reported in 15 of the patients participating in SPPs, of which 3 have been reported as

serious adverse reactions (SARs) which were submitted as Suspected Unexpected Serious Adverse Reactions (SUSARs).

Preliminary PK data available from completed studies (LOXO-RET-18014 and LOXO-RET-18015) in healthy subjects indicate that LOXO-292 has an estimated apparent terminal elimination half-life ($t_{½}$) of approximately 24 hours after a single dose.

Refer to the current IB[1] for detailed and updated background clinical study information on LOXO-292.

1.4. Study Rationale

LOXO-292 has pH-dependent solubility and its PK can be affected by agents that modify gastric pH such as proton pump inhibitors (eg, omeprazole). Under fasted conditions, following a single dose of 160 mg LOXO-292 administered to 20 omeprazole-treated healthy volunteers, the area under the concentration-time curve (AUC) and C_{max} of LOXO-292 were approximately 69% to 88% lower than following administration of LOXO-292 under fasted conditions without omeprazole. The effect of an H2 antagonist on the PK of LOXO-292 has not been tested.

In contrast to omeprazole, which is an irreversible inhibitor of gastric acid secretion, ranitidine has a shorter duration of action. This study will test the effect of ranitidine when given 10 hours before and 2 hours after the dose of LOXO-292.

The effect of omeprazole on the PK of LOXO-292 is reduced or eliminated when LOXO-292 is given with a high-calorie, high-fat meal. The AUC of LOXO-292 following administration of a single dose of 160 mg with a high-calorie, high-fat meal to 20 omeprazole-treated healthy volunteers was approximately 2% higher than following 160 mg LOXO-292 given under fasted conditions without omeprazole, although C_{max} was approximately 49% lower. Therefore, during Period 3, LOXO-292 will be administered with a low-fat meal.

To determine if the effect of agents that modify gastric pH on the PK of LOXO-292 can be reduced by various antacid dosing regimens, this study will evaluate the effect of multiple doses of an H2 antagonist (ranitidine) administered with a single dose of LOXO-292 administered under fasted conditions and the effect of multiple-doses of a proton pump inhibitor (PPI) (omeprazole) administered with a single dose of LOXO-292 given with a low-fat meal on the PK of LOXO-292 in healthy adult subjects.

1.5. Benefit-risk Assessment

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-292 may be found in the current IB.[1]

The dose of ranitidine administered in this study is not anticipated to induce any significant potential risk or benefit to subjects participating in this study, as the multiple doses are administered according to the dosing recommendations found in the full prescribing information for ranitidine.[5]

The dose of omeprazole administered in this study is not anticipated to induce any significant potential risk or benefit to subjects participating in this study, as the multiple doses are administered according to the dosing recommendations found in the full prescribing information for omeprazole.[6]

The safety monitoring practices employed by this protocol (ie, 12-lead electrocardiogram [ECG], vital signs, clinical laboratory tests, AE questioning, and physical examinations [PEs]) are adequate to protect the subjects' safety.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The objectives of this study are:

Primary:

- To assess the effect of multiple doses of an H2 antagonist (ranitidine) administered with a single dose of LOXO-292 on the PK of LOXO-292 under fasted conditions in healthy adult subjects.
- To assess the effect of multiple doses of a PPI (omeprazole) administered with a single dose of LOXO-292 on the PK of LOXO-292 given with a low-fat meal in healthy adult subjects.

Secondary:

- To determine the safety and tolerability of a single dose of LOXO-292 under fasted conditions alone, in combination with an H2 antagonist (ranitidine) under fasted conditions, and in combination with a PPI (omeprazole) given with a low-fat meal in healthy adult subjects.

2.2. Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-292 (as appropriate): area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t}), area under the concentration time curve extrapolated to infinity ($AUC_{0-\infty}$), extrapolation for area under the concentration time curve ($\%AUC_{extrap}$), maximum plasma concentration (C_{max}), t_{max}, elimination rate constant (λ_z), apparent systemic clearance (CL/F), and apparent terminal elimination half-life ($t_{½}$).

Safety and tolerability will be assessed by monitoring AEs, performing PEs and clinical laboratory tests, measuring vital signs, and recording ECGs.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an open label, 3-period, fixed sequence study.

In Period 1, a single oral dose of LOXO-292 will be administered under fasted conditions. On Day 1 of Period 1, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 1.

In Period 2, multiple oral doses of ranitidine will be administered twice daily from Day 8 until Day 18 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 12 under fasted conditions. On Day 12, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. On Day 12, ranitidine will be administered 2 hours (± 10 minutes) after the LOXO-292 dose. On Days 8-11 and 13-18, the morning dose of ranitidine will be administered (with breakfast) approximately 2 hours (± 1 hour) after the planned or actual time of the Day 12 LOXO-292 dose and the evening dose of ranitidine will be administered (with a light meal/snack) approximately 10 hours (± 1 hour) prior to the planned or actual time of the Day 12 LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 12.

In Period 3, multiple oral doses of omeprazole will be administered once daily from Day 19 until Day 29 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 23 with a low-fat meal. On Day 23, omeprazole and a single oral dose of 160 mg of LOXO-292 will be coadministered within 30 minutes of the start of a low-fat meal, which will be entirely consumed within 30 minutes. On Days 19 - 22 and 24 - 29, omeprazole will be administered following a fast of 2 hours prior to and 1 hour after the omeprazole dose (Note: omeprazole will be administered at approximately the actual time of the Day 12 LOXO-292 dosing). Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 23.

There will be a washout period of 7 days between the LOXO-292 dose in Period 1 and the first dose of ranitidine in Period 2 and a washout period of 7 days between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 30 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. A follow-up phone call will occur for all subjects who received at least 1 dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET.

The start of the study is defined as the date the first subject who is enrolled in the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned a dose of study drug; this definition excludes screen failure subjects.

In this study, PEs, 12-lead ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, complete blood count (CBC), and urinalysis (UA; Appendix 2) and recording of concomitant medications will be performed at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 4). AEs and SAEs will be collected beginning at informed consent. AEs will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

Blood samples for LOXO-292 PK analysis will be obtained in each period through 168 hours following LOXO-292 administration. A study flow chart is presented in Appendix 4. Study completion is defined as the time of the last subject's follow-up phone call.

3.2. Discussion of Study Design

This study will evaluate the effect of multiple doses of an H2 antagonist (ranitidine) administered under fasted conditions and the effect of effect of multiple-doses of a PPI (omeprazole) given with a low-fat meal on the PK of LOXO-292 in healthy adult subjects.

Gastric pH can alter the absorption of acidic and basic drugs and nonclinical study results indicate that LOXO-292 may be sensitive to gastric pH. The Food and Drug Administration (FDA) has recently published a review on the topic and has encouraged studies to address the effects of coadministration of gastric pH modifiers on oral exposure.[7] Thus, a PPI and an H2 antagonist were chosen to be studied.

Subjects will participate in 3 periods in a fixed sequence. The washout period of 7 days between LOXO-292 doses is considered sufficient to prevent carryover effects of the treatments. However, as omeprazole may have a prolong effect on acid secretion due to the irreversible nature of omeprazole binding to H+/K+ ATPase pump, the omeprazole treatment portion will be conducted only in Period 3 to ensure the effect of a PPI with a low-fat meal can be assessed without confounding factors.

3.3. Selection of Doses in the Study

LOXO-292

An oral dose has been selected for this study because this is the intended clinical route of administration. The dose of 160 mg of LOXO-292 was selected based on clinical study results and its observed PK profile. The 160 mg dose is expected to ensure sufficient quantifiable plasma concentrations of LOXO-292 for determination of systemic PK exposure. In a Phase 1/2 clinical study in cancer patients (LOXO-RET-17001), 160 mg of LOXO-292 dosed twice daily has been evaluated and has been selected for further testing in a larger number of cancer patients to evaluate its safety and efficacy.

Omeprazole:

A dose of 40 mg omeprazole daily is within the recommended dose as prescribed in the labeling. In addition, multiple doses for 4 consecutive days prior to LOXO-292 administration will ensure maximum inhibition of acid secretion by omeprazole, because the inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after 4 days.

Ranitidine:

A dose of 150 mg ranitidine twice daily is within the recommended dose as prescribed in the labeling. In addition, multiple doses for 4 consecutive days prior to LOXO-292 administration will mimic real-life scenarios of patients taking H2 antagonists in the intended patient population.

4. SELECTION OF STUDY POPULATION

The study will be conducted in healthy subjects. As per the recommendations of the FDA in the draft guidance on clinical drug interaction studies,[8] drug interaction studies can be carried out in healthy volunteers assuming that findings in healthy subjects can be used to predict findings in the intended patient population.

4.1. Screening Procedures

The following screening procedures will be performed for all potential subjects at a visit conducted within 28 days of study entry (ie, prior to Check-in [Day -1]):

1. Informed consent
2. Demographic data
3. Medical history
4. Inclusion/exclusion criteria
5. Height, weight, and body mass index (BMI)
6. Complete PE (Section 7.2.5)

7. Screens for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), and human immunodeficiency virus (HIV) antibody (Appendix 2)
8. Screen for selected drugs of abuse (including cotinine) and an alcohol breath test (Appendix 2)
9. Twelve-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
10. Vital signs (including oral temperature, respiratory rate, and supine blood pressure [BP] and heart rate [HR; measured after the subject has been supine for at least 5 minutes]) (Section 7.2.3)
11. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, creatine kinase (CK), CBC, and UA; Appendix 2)
12. Hemoglobin A1c test (Appendix 2)
13. Thyroid stimulating hormone (TSH) test (Appendix 2)
14. How Do You Feel? inquiry and AE and concomitant medication evaluations (Section 7.2.1)
15. Serum pregnancy test (for females only; Appendix 2)
16. Follicle-stimulating hormone (FSH) test (for postmenopausal females only; Appendix 2)

4.2. Check-in Procedures (Day -1)

At Check-in (Day -1), subjects will report to the CRU and the following procedures will be performed:

1. AEs
2. Interim medical history
3. Weight and BMI
4. Abbreviated PE (Section 7.2.5)
5. Review of inclusion/exclusion criteria
6. Screen for selected drugs of abuse (including cotinine) and an alcohol breath test (Appendix 2)
7. Twelve-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
8. Vital signs (including oral temperature, respiratory rate, and supine BP and HR [measured after the subject has been supine for at least 5 minutes]) (Section 7.2.3)

9. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], including CK, coagulation parameters, CBC, and UA; Appendix 2)
10. TSH test (Appendix 2)
11. How Do You Feel? inquiry and concomitant medication evaluations (Section 7.2.1)
12. Serum pregnancy test (for females only; Appendix 2)
13. Follicle-stimulating hormone (FSH) test (for postmenopausal females only; Appendix 2)
14. Compliance with concomitant medications and exclusionary restrictions (Section 6)

For subjects to continue their participation in the study, the inclusion/exclusion criteria must continue to be met at Day -1 (as appropriate; Section 4). In addition, continued compliance with concomitant medication and other restrictions will be verified.

The Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. Prior to dosing, the Sponsor will provide approval of subjects selected for enrollment by the Investigator (or designee).

Subjects who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the discretion of the Investigator (or designee) or Sponsor.

4.3. Inclusion Criteria

Subjects who meet the following criteria at Screening and Check-in (Day -1), unless otherwise specified, may be included in the study:

1. Males, and females of nonchildbearing potential, between 18 and 55 years of age, inclusive, at Screening
2. Within BMI range 18.5 to 32.0 kg/m^2, inclusive
3. In good health, determined by no clinically significant findings from medical history, PE, 12-lead ECG, vital signs measurements, or clinical laboratory evaluations (Appendix 4) at Screening or Check-in as assessed by the Investigator (or designee)
4. Females of nonchildbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to study drug administration) or postmenopausal (defined as at least 12 months postcessation of menses without an alternative medical cause). Postmenopausal status will be confirmed with a screening serum FSH level $\geq$ 40 mIU/mL. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1)

5. Males who are capable of fathering a child must agree to use one of the following methods of contraception from the time of the dose administration through 6 months after the last dose of LOXO-292 administration:

    - Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1). If documentation is not available, male subjects must follow one of the contraception methods below:
        - Male condom with spermicide, and
        - For a female partner of male study participant:
            - Intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
            - Established use of oral, implanted, transdermal, intravaginal, or hormonal method of contraception associated with inhibition of ovulation; or
            - Bilateral tubal ligation.

    Males who practice true abstinence because of a lifestyle choice (ie, do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject is abstinent at the time of signing the ICF but becomes sexually active through EOS, he must agree to use contraception as described above.

    For male subjects, sexual intercourse with female partners who are pregnant, or breastfeeding should be avoided. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after administration of study drug.

    For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

6. Able to understand and provide written informed consent
7. Able to comply with all study procedures, including the 30-night stay at the CRU and follow-up phone call

4.4. Exclusion Criteria

The following will exclude potential subjects from the study:

1. History or presence of any of the following, deemed clinically significant by the Investigator (or designee), and/or Sponsor:
    a. liver disease

b. pancreatitis
c. peptic ulcer disease
d. intestinal malabsorption
e. gastric reduction surgery
f. history or presence of clinically significant cardiovascular disease:
    i. Myocardial infarction or cerebrovascular thromboembolism within 6 months prior to the first dose administration (Day 1)
    ii. Symptomatic angina pectoris within 6 months prior to the first dose administration (Day 1)
    iii. New York Heart Association Class ≥ 2 congestive heart failure within 6 months prior to the first dose administration (Day 1)
    iv. Congenital prolonged QT syndrome
    v. Ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
    vi. Arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention
    vii. Ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)
    viii. Significant screening ECG abnormalities:
        1. Left bundle branch block
        2. Second degree atrioventricular (AV) block, type 2, or third-degree AV block
        3. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec

2. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital signs at Screening, Check-in (Day -1), or prior to dosing on Day 1, including:
    - Oral body temperature > 37.5°C
    - Heart rate < 50 or > 99 bpm
    - Systolic BP < 89 or > 139 mmHg
    - Diastolic BP < 50 or > 89 mmHg

    For these parameters, out-of-range values that are not clinically significant (as determined by the Investigator or designee) may be repeated twice during Screening, Check-in (Day -1), and predose on Day 1. Note: Rechecks of HR and BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for

participation in the study based on rechecked HR and/or BP values if the values fall within the ranges stated above.

3. Abnormal laboratory values (CBC, UA, clinical chemistry panel [fasted at least 8 hours], excluding those further defined in exclusion criteria 5, 6, and 7 below) determined to be clinically significant by the Investigator (or designee), and Sponsor at Screening and/or Check-in (Day -1) as confirmed by repeat assessment
4. Clinically significant abnormality, as determined by the Investigator (or designee), from PE at Screening and/or Check-in (Day -1)
5. Abnormal LFTs, as defined by AST, ALT, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or Check-in. Rechecks of LFTs, amylase, and lipase will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges.
6. Any clinically significant deviations from normal ranges in CK unless approved by the Investigator (or designee) and Sponsor. Rechecks of CK will be permitted up to 2 times to confirm eligibility for study participation if the out of range values are stable or trending down and the Investigator (or designee) and the Sponsor deem that the results are not clinically significant and will not impact study conduct.
7. Estimated creatinine clearance ≤ 90 mL/minute at Screening or Check-in (Day -1) calculated using the Cockcroft-Gault equation
8. Positive serologic test for hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at Screening. Subjects who are positive for hepatitis B virus, HCV, or HIV by antibody will require confirmation by polymerase chain reaction (PCR) before enrollment to detect presence of active virus. Subjects who are PCR positive or for whom a PCR is unable to be obtained will not be eligible.
9. Subjects with known ongoing alcohol and/or drug abuse within 2 years prior to Screening, or evidence of such abuse as indicated by the laboratory assays and alcohol breath tests conducted during Screening and/or at Check-in (Day -1)
10. Consumption of grapefruit/grapefruit juice or Seville oranges or its juice within 7 days prior to Check-in (Day -1) and through EOT or ET
11. Consumption of alcohol or caffeine containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee)
12. Positive alcohol breath test result at Screening or Check-in (Day -1)
13. Positive urine screen for drugs of abuse at Screening or Check-in (Day -1)
14. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET

15. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee)
16. Participation in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to the first dose administration (Day 1)
17. Use or intention to use any prescription or over-the-counter medications (including but not limited to any moderate or strong cytochrome P450 (CYP)3A4 and/or CYP3A5 inhibitors or inducers, strong P-gp inhibitors, proton pump inhibitors [with the exception of omeprazole administered for the purposes of this study/in accordance with the Protocol], antacids, H2-receptor antagonists [with the exception of ranitidine administered for the purposes of this study/in accordance with the Protocol], and drugs that prolong QT/QTc interval, herbal products, natural or herbal supplements) within 14 days prior to the first dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor
18. History of a major surgical procedure within 30 days prior to Screening
19. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator, would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk
20. History of gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition that might, in the opinion of the Investigator or designee, and as confirmed by the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-292
21. Poor peripheral venous access
22. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening
23. Receipt of blood products within 2 months prior to Check-in (Day -1)
24. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET
25. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin)
26. History of diabetes mellitus; hemoglobin A1c $\geq$ 6.5%
27. History of congenital nonhemolytic hyperbilirubinemia (eg, Gilbert's syndrome)

28. Have previously completed or withdrawn from any other study investigating LOXO-292, and have previously received the investigational product
29. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator (or designee), and as confirmed by the Sponsor, within the 30 days prior to the first dosing and through EOT or ET
30. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study

4.5. Subject Number and Identification

Subject number will consist of 6 digits in which the first set of 3 digits will identify the site and the second set of 3 digits will identify the subject (eg, 001-101). For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced. Replacement subjects will be assigned a subject number by adding 100 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-201 replaces Subject Number 001-101).

4.6. Removal of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator (or designee) may remove a subject from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn because of the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, intake of nonpermitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of withdrawal will immediately be made to the Study Monitor. In case of withdrawal, efforts will be made to perform all final study day assessments (Appendix 4). The date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's electronic Case Report Form (eCRF). All withdrawn subjects with AEs that are assessed as related to study drug and which are ongoing at ET may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator (or designee) and confirmed by the Sponsor.

The entire study may be discontinued at the discretion of the Investigator (or designee) or Sponsor, based on the occurrence of the following:

- Adverse events unknown to date with respect to their nature, severity, and/or duration;
- Increased frequency and/or severity and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;
- Cancellation of drug development.

In the event that the study is terminated early, the Sponsor or its designee will provide specific guidance to the CRU regarding the end of study procedures.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drug for Period 1 (Table 1) Period 2 (Table 2), and Period 3 (Table 3).

Table 1 Study Drug – Period 1

Study Drug	LOXO-292
Form	Capsule[a]
Strength	80 mg
Supplier	Loxo Oncology, Inc.
Manufacturer	Avista Pharma Solutions, Inc.

[a]Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.

Table 2 Study Drug – Period 2

Study Drug	LOXO-292	Ranitidine
Form	Capsule[a]	Tablet
Strength	80 mg	150 mg
Supplier	Loxo Oncology, Inc.	Covance
Manufacturer	Avista Pharma Solutions, Inc.	Ajanta Pharma Limited

[a]Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.

Table 3 Study Drug – Period 3

Study Drug	LOXO-292	Omeprazole
Form	Capsule[a]	40 mg
Strength	80 mg	capsule
Supplier	Loxo Oncology, Inc.	Covance
Manufacturer	Avista Pharma Solutions, Inc.	Sandoz Inc

[a]Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.

The capsules containing 80 mg LOXO-292 will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificate of Analysis. It will be provided in high density polyethylene bottles and stored according to the instructions on the label.

Study drugs will be stored at the CRU in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The study drugs will be stored in accordance with the labeling. The study drugs will be transferred from bulk supplies into the subject's dose container by qualified CRU employees. Each unit dose container will be appropriately labeled.

5.2. Study Treatment Administration

LOXO-292 will be supplied by Loxo Oncology as 80 mg capsules for oral administration. Ranitidine will be supplied by Covance as 150 mg tablets for oral administration. Omeprazole will be supplied by Covance as 40 mg delayed-release capsules for oral administration.

In Period 1, a single oral dose of LOXO-292 will be administered under fasted conditions. On Day 1 of Period 1, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 1.

In Period 2, multiple oral doses of ranitidine will be administered twice daily from Day 8 until Day 18 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 12 under fasted conditions. On Day 12, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. On Day 12, ranitidine will be administered 2 hours (± 10 minutes) after the LOXO-292 dose. On Days 8 - 11 and 13 - 18, the morning dose of ranitidine will be administered (with breakfast) approximately 2 hours (± 1 hour) after the planned or actual time of the Day 12 LOXO-292 dose and the evening dose of ranitidine will be administered (with a light meal/snack) approximately 10 hours (± 1 hour) prior to the planned or actual time of the Day 12 LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 12.

In Period 3, multiple oral doses of omeprazole will be administered once daily from Day 19 until Day 29 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 23 with a low-fat meal. On Day 23, omeprazole and a single oral dose of 160 mg of LOXO-292 will be coadministered within 30 minutes of the start of a low-fat meal, which will be entirely consumed within 30 minutes. On Days 19 - 22 and 24 - 29, omeprazole will be administered following a fast of 2 hours prior to and 1 hour after the omeprazole dose (Note: omeprazole will be administered at approximately the actual time of the Day 12 LOXO-292 dosing). Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 23.

All study drugs will be administered orally with approximately 240 mL of water. An additional 100 mL of water may be administered if needed.

Each unit dose will be prepared by qualified clinical staff. Each unit dose container will be appropriately labeled.

Appropriate unit dose(s), as described above, will be administered to consecutively numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at a specific time, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule.

For each dose, the subject's actual dose time will be recorded in the source documents and transcribed into the eCRF.

Subjects will be instructed not to crush, split, or chew the study drugs.

Subjects will not lay supine for 4 hours following LOXO-292 dose administration, except as necessitated by the occurrence of an AE(s) and/or study procedure(s).

5.3. Randomization

This is an open-label study.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified CRU staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of LOXO-292, omeprazole and ranitidine will be performed as appropriate.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of LOXO-292 capsules, omeprazole capsules, and ranitidine tablets received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused LOXO-292 capsules will be returned to the Sponsor or disposed of by the CRU, per the Sponsor's written instructions. Omeprazole capsules and ranitidine tablets will be disposed of by the CRU in accordance with the CRUs standard operating procedures.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from participation in any other investigational study drug trial in which receipt of any investigational drug occurs within 5 half-lives (if known) or 30 days, whichever is longer, prior to dose administration (Day 1).

All prescription and over-the-counter medications (including, herbal products, natural or herbal supplements) are prohibited for 14 days prior to dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee), and Sponsor. This includes but is not limited to: Moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers, strong P-gp inhibitors, proton pump inhibitors (with the exception of omeprazole administered for the purposes of this study/in accordance with the protocol), antacids, H2-receptor antagonists (with the exception of ranitidine administered for the purposes of this study/in accordance with the protocol), and drugs that prolong QT/QTc interval.

Any medication taken by a subject during the course of the study, including details of its dosage, administration, and the reason for its use, will be documented in the eCRF.

The administration of any concomitant medication during the study is prohibited without prior approval of the Investigator (or designee), and Sponsor, unless its use is deemed necessary in a medical emergency. In this case, the use of the concomitant medication will be reported as soon as is practical.

6.2. Diet, Fluid, and Activity Control

Subjects are required to refrain from use of tobacco, smoking cessation products, and nicotine-containing products within 3 months prior to Screening through EOT or ET.

Consumption of foods or beverages containing grapefruit/grapefruit juice or Seville oranges or its juice within 7 days prior to Check-in (Day -1) and through EOT or ET will not be allowed unless deemed acceptable by the Investigator (or designee), and Sponsor.

Consumption of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET will not be allowed unless deemed acceptable by the Investigator (or designee), and Sponsor.

Subjects will refrain from strenuous exercise from 5 days prior to Check-in (Day -1) and during the period of confinement at the CRU and will otherwise maintain their normal level of physical activity through EOT or ET (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion).

While confined at the CRU, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

In Period 1, a single oral dose of LOXO-292 will be administered under fasted conditions. On Day 1 of Period 1, a single oral dose of 160 mg of LOXO-292 will be administered following a

fast of 10 hours prior to and 4 hours after the LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 1.

In Period 2, multiple oral doses of ranitidine will be administered twice daily from Day 8 until Day 18 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 12 under fasted conditions. On Day 12, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. On Day 12, ranitidine will be administered 2 hours (± 10 minutes) after the LOXO-292 dose. On Days 8 - 11 and 13 - 18, the morning dose of ranitidine will be administered (with breakfast) approximately 2 hours (± 1 hour) after the planned or actual time of the Day 12 LOXO-292 dose and the evening dose of ranitidine will be administered (with a light meal/snack) approximately 10 hours (± 1 hour) prior to the planned or actual time of the Day 12 LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 12.

In Period 3, multiple oral doses of omeprazole will be administered once daily from Day 19 until Day 29 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 23 with a low-fat meal. On Day 23, omeprazole and a single oral dose of 160 mg of LOXO-292 will be coadministered within 30 minutes of the start of a low-fat meal, which will be entirely consumed within 30 minutes. On Days 19 - 22 and 24 - 29, omeprazole will be administered following a fast of 2 hours prior to and 1 hour after the omeprazole dose (Note: omeprazole will be administered at approximately the actual time of the Day 12 LOXO-292 dosing). Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 23.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of LOXO-292 plasma levels will be collected at the timepoints specified in Appendix 4. The exact time of the study drug administration and the actual time of blood sampling for PK analysis will be recorded on the eCRF.

Processing, storage, and shipping instructions for these PK blood will be provided in a separate Laboratory Manual. The number of blood samples and total blood volume required for PK testing and protein binding is presented in Appendix 3.

7.1.2. Analytical Methodology

Concentrations of LOXO-292 in plasma will be determined using a validated bioanalytical method. Specifics of the bioanalytical methods will be provided in a separate document.

7.2. Safety and Tolerability Assessments

Safety evaluations may be repeated at the discretion of the Investigator (or designee) or Sponsor.

Every effort will be made to schedule and perform the procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and any other procedures to be performed at the same timepoint. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- Dosing
- Pharmacokinetic blood sampling
- Vital signs assessments
- ECG
- Blood and urine samples for clinical laboratories
- PE

7.2.1. Adverse Events

Adverse event definitions; assignment of severity, causality, action taken, and outcome; and procedures for reporting SAEs are detailed in Appendix 1.

Subjects will be asked a nonleading HDYF? question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the timepoints specified in Appendix 4 (ie, at Screening [after the ICF is signed], at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days). Subjects will also be encouraged to voluntarily report AEs occurring at any other time through the EOS.

AEs, whether volunteered, identified by the subject's responses to HDYF? inquiries, or noted on PE, ECG, vital signs assessments, or laboratory tests, will be recorded throughout the study (ie, from signing of the ICF until EOS [or ET if the subject discontinues from the study and does not complete a follow-up phone call]), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

Unless a subject withdraws consent or is withdrawn from the study and does not complete the follow-up phone call, all subjects must be followed until EOS. Subjects with AEs that are assessed as related to study drug by the Investigator (or designee) which are ongoing at EOS may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as

judged by the Investigator or designee and confirmed by the Sponsor. The Investigator (or designee) should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that additional safety tests be performed.

Subjects will receive a follow-up phone call 7 days (± 2 days) after EOT or ET to determine if any AE has occurred since the EOT or ET visit.

At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator (or designee).

Any event that meets the criteria of a SUSAR will be reported to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to CRU policy by the Investigator (or designee) and to regulatory authorities by the Sponsor (or Sponsor designee) according to regulatory authority requirements. Refer to Reference Safety Information in the current IB[1] for LOXO-292 for expected adverse reactions.

7.2.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations (clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CBC, TSH, hemoglobin A1c [Screening only], and UA) will be collected at the timepoints specified in Appendix 4.

Screens for HCV antibody, HBsAg, and HIV antibody will be performed at Screening. A urine drug screen for selected drugs of abuse (including cotinine) and an alcohol breath test will be performed at Screening and repeated at Check-in (Day -1) for all subjects. A serum qualitative pregnancy test (females only) and an FSH test (postmenopausal females only) will be performed at the timepoints specified in Appendix 4.

The number of blood samples and total blood volume required for clinical laboratory evaluations is presented in Appendix 3. A list of the specific evaluation is in Appendix 2.

7.2.3. Vital Signs

Vital signs (including oral temperature, respiratory rate, and supine BP and HR) will be obtained at the timepoints specified in Appendix 4.

Blood pressure and HR measurements should be performed using the same arm for each reading and measurements should be taken after the subject has been resting in the supine position for at least 5 minutes.

When vital signs assessments are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vital signs will be obtained prior to and as close as possible to the scheduled blood draw.

7.2.4. 12-Lead Electrocardiogram

A 12-lead ECG (including PR, RR, QRS, and QT interval parameters) will be obtained after the subject has been resting for at least 10 minutes in the supine position at the timepoints specified

in Appendix 4. The QT interval will be corrected for HR by Fridericia's ($QTcF = QT/[RR]^{1/3}$) formula.

When 12-lead ECGs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the 12-lead ECGs will be obtained prior to and as close as possible to the scheduled blood draw.

7.2.5. Physical Examination

A complete or abbreviated PE will be performed at the timepoints specified in Appendix 4. Complete PEs will evaluate general appearance and the following body systems/organs: dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; lymphatic; musculoskeletal/extremities; and neurological. Weight and height will be reported (height only reported during Screening).

Abbreviated PEs will evaluate general appearance and the following body systems/organs: dermatological; pulmonary; cardiovascular; abdominal; and neurological.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size.

CCI [redacted]

8.2. Analysis Populations

8.2.1. Study Populations

The **PK Population** will consist of all subjects who have received a dose of LOXO-292, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed.

The **Safety Population** will consist of all subjects who have received at least 1 dose of study drug. Subjects will be classified into groups based on actual treatment received.

8.3. Pharmacokinetic Analysis

Serial PK blood samples for the analysis of plasma LOXO-292 concentrations will be collected from predose through 168 hours postdose.

Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of LOXO-292 (as appropriate):

AUC_{0-t}	area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage extrapolation for AUC
C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
λ_Z	apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus-time profile during the terminal phase
CL/F	apparent systemic clearance
$t_{½}$	apparent terminal elimination half-life (whenever possible), where $t_{½}$ = natural log (ln)(2)/ λ_Z

Additionally, the number of points used to estimate λ_Z will be presented in a listing.

Pharmacokinetic calculations will be performed using commercial software such as Phoenix™ WinNonlin® Version 6.4 or higher (Certara USA Inc.).

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

Pharmacokinetic analysis will use actual times as recorded on the eCRF. All statistical analysis will be performed using SAS® Version 9.3 or greater. More details on the analyses will be included in the SAP.

8.3.1. Descriptive Analysis

Plasma concentrations and PK parameters will be summarized with descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum).

8.3.2. Analysis of Variance (ANOVA)

The primary analysis planned for this study is an ANOVA model that includes treatment as a fixed-effect and subject as a random-effect. CCI

[redacted]

8.4. Safety Analysis

All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory results, PE results, concomitant medications, and ECG interpretations, will be tabulated and summarized where possible, using descriptive methodology, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last nonmissing measurement before administration of LOXO-292 in each period. No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug Global B3, 01 March 2019). The incidence of AEs will be presented by severity and by relationship to study drug as determined by the Investigator (see Appendix 1 for AE reporting). All TEAEs will be summarized by system organ class and preferred term, using Medical Dictionary for Regulatory Activities (MedDRA Version 22.0).

8.5. Data Handling and Record Keeping

Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by a CRU staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

The Data Management Plan will be approved by the Sponsor.

Data will be validated during data entry by the CRU and verified by the Study Monitor. Data will then be reviewed by the data management group to resolve any outstanding issues. Listings will be generated after the database is cleaned by data management and will be reviewed by the Covance scientific team. The eCRF and ancillary data will be converted into final SAS® datasets following Study Data Tabulation Model or client-provided specifications. The final datasets structure will be verified using Web Submission Data Manager®, while the dataset content will be peer reviewed by an independent programmer.

The tables, figures, and listings (TFLs) will be programmed per the final SAP. All TFLs will be peer reviewed by an independent programmer. In addition, draft TFLs will be reviewed by the Covance scientific team during the dry run and data review meetings.

The peer review will be performed by independent programmers following the quality control process and programming checklists.

8.6. Quality Control and Quality Assurance

Quality control and quality assurance will be performed according to Covance standard operating procedures or per client request and as applicable, according to the contract between Covance and the Sponsor.

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator (or designee).

There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator (or designee), and the IRB (see Form FDA 1572).

9.2. Site Initiation Visit/Investigator Meeting

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator (or designee) and appropriate clinical staff to familiarize the Investigator (or designee) and clinical staff with the materials necessary for conducting the clinical study.

9.3. Disclosure

All information provided regarding the study, as well as all information collected/documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, in part or in total (eg, articles in journals or newspapers, oral presentations, abstracts) by the Investigator (or designee) or their representative(s), shall require prior notification and review, within a reasonable timeframe, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

9.4. Monitoring

The Sponsor will designate a Study Monitor who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Sponsor's Study Monitor will visit the CRU at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator (or designee) and Investigator's staff will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

9.5. Institutional Review Board

In accordance with US Title 21 Code of Federal Regulations (CFR) 56, the protocol, advertisement, ICF, and other information provided to subjects will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the Investigator (or designee) to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator (or designee).

The IRB will be informed by the Investigator (or designee) of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the Investigator (or designee). If requested, the Investigator (or designee) will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The Investigator (or designee) will provide the IRB with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's (or designee's) participation in the study.

9.6. Informed Consent

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The ICF will be approved (along with the protocol) by the IRB and will be acceptable to the Sponsor.

The Investigator (or designee) will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the IRB and signed by the subject prior to protocol-specific procedures being performed.

The subject will sign 2 copies of the ICF. One copy will be given to the subject, and the other will be maintained with the subject's records.

9.7. Records

The results from data collected at Screening and during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers.

The completed eCRFs will be transferred to the Sponsor (or designee). Copies of each eCRF will be retained by the Investigator (or designee). All source documents, records, and reports will be retained by the CRU in accordance with 21 CFR 312.62(c).

All primary data, or copies thereof (eg, laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the CRU archives.

9.8. Reference to Declaration of Helsinki/Basic Principles

The study procedures outlined in this protocol will be conducted in accordance with the US CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), Applications for FDA Approval to Market a New Drug (21 CFR 314), and Radioactive Drugs for Certain Research Uses (21 CFR 361.1), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable International Council for Harmonisation Guidelines, are commonly known as Good Clinical Practices, which are consistent with the Declaration of Helsinki.

9.9. Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

10. REFERENCES

1. Loxo Oncology, Inc. LOXO-292 – Investigator's Brochure (Version 5.0). 05 June 2019.
2. Drilon, A, Subbiah, V, Oxnard G, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with *RET*-altered cancers. J Clin Oncol 2018;36(suppl): abstr 102.
3. Oxnard G, Subbiah V, Park K, et al. Clinical activity of LOXO-292, a highly selective RET inhibitor, in patients with RET fusion + non-small cell lung cancer. J Thoracic Oncol 1018;13(10):S349-50.
4. Wirth LJ, Cabanillas ME, Sherman EJ, et al. Clinical activity of LOXO-292, a highly selective RET inhibitor, in patients with RET-altered thyroid cancers: an update from ASCO 2018. 88th Meeting of the American Thyroid Association, 3-7 Oct 2018.
5. Ranitidine - ranitidine tablets [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; 2016.
6. Omeprazole – omeprazole capsule delayed release [package insert]. Princeton, NJ: Sandoz Inc; 2018.
7. Zhang L, Wu F, Lee SC, et al. pH-dependent drug-drug interactions for weak base drugs: potential implications for new drug development. Clin Pharmacol Ther 2014;96:266-77.
8. Food and Drug Administration: Center for Drug Evaluation and Research (CDER). Guidance for Industry: Clinical Drug Interaction Studies (Oct 2017).

11. APPENDICES

Appendix 1: Adverse Event Reporting

Adverse Events

Definition of Adverse Events

An adverse event (AE; or adverse experience) is defined as any untoward medical occurrence experienced by a patient or healthy subject, whether or not considered drug related by the Investigator (or designee). A treatment-emergent AE is an AE that is reported after a dose of study drug.

The following are all AEs:

- Unfavorable changes in general condition;
- Subjective or objective signs/symptoms;
- Concomitant diseases or accidents;
- Clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study.

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities that are deemed clinically significant by the Investigator or designee), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance.

Categorization of Adverse Events

The severity of AEs will be categorized based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as follows:

- **Grade 1 Mild:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2 Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*
- **Grade 3 Severe or medically significant but not immediately life threatening:** Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- **Grade 4 Life-threatening consequences**: Urgent intervention indicated
- **Grade 5 Death related to AE**

Note: Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

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

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

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 2-category system according to the following guidelines:

- **NOT RELATED** = The time course between the administration of investigational product and the occurrence or worsening of the AE rules out a causal relationship and another cause (eg, concomitant drugs, therapies, complications, comorbidities) is suspected;
- **RELATED** = The time course between administration of investigational product and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (eg, concomitant drugs, therapies, complications, comorbidities) can be identified.

An AE is associated with the use of the drug if there is a reasonable possibility that the experience may have been caused by the drug.

Pregnancy

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed through EOS or ET (if the subject discontinues from the study and does not complete a follow-up phone call) and for up to 90 days after study drug administration should be reported by the Investigator (or designee) via eFax to the Sponsor's clinical safety representative within 24 hours of being notified. The Sponsor's safety representative will then forward the Pregnancy Form to the Investigator for completion.

eFax: +1 (203) 643-2013

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed. The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor's clinical safety representative. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a serious AE (SAE; ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

Male subjects will be instructed to notify the Investigator immediately if they discover their sexual partner is pregnant. In this instance, the partner must provide written consent before pregnancy information can be collected. When a CRU becomes aware that the female partner of a male subject is pregnant, they are to contact the Investigator immediately (within 24 hours of the CRU staff becoming aware of the event) in addition to notifying the Sponsor's safety representative via eFax.

All pregnancies should be recorded on the AE eCRF, in addition to completion of the required pregnancy forms. If the Investigator suspects that a pregnancy was the result of an interaction

between the study treatment and the contraceptive method, in addition to the pregnancy the drug interaction should also be captured as a separate AE.

Definition of Serious Adverse Events

An SAE (by FDA definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience (ie, one that places the subject, in the view of the Investigator [or designee], at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- An important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Adverse Drug Reaction

An AE or suspected adverse drug reaction is considered 'unexpected' if the event is not listed in the Reference Safety Information section of the IB or if it is not listed at the specificity or severity that has been observed for an unapproved investigational medicinal product.

Reporting

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and represent events that are assessed as serious, related, and unexpected. Food and Drug Administration-reportable AEs will be reported by the CRU to the Sponsor and the responsible Institutional Review Board (IRB). Final determination of whether an event represents a SUSAR will be the responsibility of the Sponsor.

Within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported, and within 24 hours of any SAE (regardless of whether the event is assessed as related or unrelated to study drug) being first recognized or reported, the Sponsor's clinical safety representative will be notified by the Investigator or designee in writing (eg, facsimile) using the following eFax number or email:

eFax: +1 (203) 643-2013

email: safety@loxooncology.com

To report the SAE, the completed report form should be sent by eFax to the Sponsor's clinical safety representative within 24 hours of awareness. Incoming reports are reviewed during normal business hours. Additional reporting instructions and the SAE Report Form are provided in the Study Manual.

The IRB will be notified of any FDA-reportable AE within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

Appendix 2: Clinical Laboratory Evaluations

Clinical Chemistry Panel (Fasted):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Amylase
Aspartate aminotransferase
Bilirubin (direct and total)
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatine kinase
Creatinine
Glucose
Iron
Lipase
Magnesium
Phosphorus
Potassium
Sodium
Total protein
Triglycerides
Uric acid

Complete Blood Count:
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential (percent and absolute):
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils

Other Tests:
Hemoglobin A1c
Thyroid-stimulating hormone

Coagulation Parameters:
Activated partial thrombin time
Partial thromboplastin time
Prothrombin time
International normalized ratio

Serology:
Human immunodeficiency virus antibody
Hepatitis B surface antigen
Hepatitis C virus antibody

Urine Drug Screen:
Including but not limited to the following:
Alcohol (ethanol) (breath test)
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic examination including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

For Female Subjects only:
Pregnancy test (serum qualitative)
Follicle-stimulating hormone (postmenopausal females only)

Estimated Creatinine Clearance

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Purpose	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	4	1	4
Hemoglobin A1c	4	1	4
Primary Pharmacokinetic (PK) Sampling	4	60	240
Clinical Laboratory Tests:			
Complete Blood Count	4	10	40
Clinical Chemistry	4	10	40
Coagulation Parameters	3	10	30
Serum Pregnancy Test (females only)	4	3	12
Serum Follicle-stimulating Hormone Test (postmenopausal females only)	4	2	8
Thyroid-stimulating Hormone	4	2	8
		Total:	**386 mL**

Appendix 4: Schedule of Assessments

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Period 1			Period 2					Period 3					Follow-up Phone Call (EOS)
			Day 1	Day 2	Day 7	Day 8	Day 11	Day 12	Day 13	Day 18	Day 19	Day 22	Day 23	Day 24	Clinic Discharge/ EOT Day 30 or ET[s]	7 (±2) days post EOT or ET[t]
Confined to the CRU		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion/Exclusion Criteria	X	X														
Informed Consent	X															
Demographics	X															
Medical History	X	X[b]														
Height/Weight/BMI	X	X[c]														
Physical Examination[d]	X	X	X					X					X		X	
12-Lead ECG[e]	X	X	X	X		X		X	X		X		X	X	X	
Vital Signs[f]	X	X	X	X		X		X	X		X		X	X	X	
HDYF? Inquiry[g]	X	X	X	X		X		X	X		X		X	X	X	X
AEs/SAEs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LOXO-292 Dosing[i]			X					X					X			
Ranitidine Dosing[j]						X (Days 8 to 18, inclusive)										
Omeprazole Dosing[k]											X (Days 19 to 29, inclusive)					
Primary PK Blood Samples[l]			X (Days 1-8)					X (Days 12-19)					X (Days 23-29)			
Clinical Laboratory Evaluations[m]	X	X		X	X		X		X	X		X		X	X	
Hepatitis and HIV Screen	X															
Hemoglobin A1c Test[n]	X															
Drug Screen[o]	X	X														
Prior and Concomitant Medications[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[q]	X	X													X	

Follicle-Stimulating Hormone Test[r]	X	X														
Thyroid-Stimulating Hormone Test	X	X														

Abbreviations: AE = adverse event; BMI = body mass index; CK = creatine kinase; CRU = Clinical Research Unit; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ET = early termination; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; ICF = Informed Consent Form; PE = physical examination; PK = pharmacokinetic; SAE = serious adverse event.

[a.] For details on study procedures, see Section 7.

[b] Interim medical history only.

[c] Weight and BMI (based on Screening height) only.

[d] A complete PE will be performed at Screening and EOT (or ET). An abbreviated PE will be performed at Check-in (Day -1) and 1 hour postdose on Days 1, 12, and 23 (1 hour post LOXO-292 dose).

[e] Electrocardiograms will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws at Screening and Day -1, Day 1 (before LOXO-292 dosing), Day 2, Day 8 (before ranitidine dosing), Day 12 (before LOXO-292 dosing), Day 13, Day 19 (before omeprazole dosing), Day 23 (before LOXO-292 dosing), Day 24, and EOT (or ET).

[f] Vital signs measurements (oral temperature, respiratory rate, and supine blood pressure and heart rate) will be obtained Screening and Day -1, Day 1 (before LOXO-292 dosing), Day 2, Day 8 (before ranitidine dosing), Day 12 (before LOXO-292 dosing), Day 13, Day 19 (before omeprazole dosing), Day 23 (before LOXO-292 dosing), Day 24, and EOT (or ET). Vital signs measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and HR will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.

[g] An HDYF? inquiry performed at Screening (after the ICF is signed), at Check-in (Day -1), at each postdose vital signs assessment, and at an appropriate time for all other days.

[h] AEs and SAEs will be collected beginning at informed consent. AEs will be recorded throughout the study (ie, from signing of the ICF until EOS, or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed by the Investigator [or designee]) as related to study procedures, or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug are to be recorded. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

[i] LOXO-292 will be administered in the morning of Days 1 and 12, following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. On Day 23, LOXO-292 will be coadministered with omeprazole within 30 minutes of the start of a low-fat meal which will be entirely consumed within 30 minutes.

[j] On Day 12, ranitidine will be administered 2 hours (± 10 minutes) after the LOXO-292 dose. On Days 8 - 11 and 13 - 18, the morning dose of ranitidine will be administered (with breakfast) approximately 2 hours (± 1 hour) after the planned or actual time of the Day 12 LOXO-292 dose and the evening dose of ranitidine will be administered (with a light meal/snack) approximately 10 hours (± 1 hour) prior to the planned or actual time of the Day 12 LOXO-292 dose.

[k] On Day 23, omeprazole and a single oral dose of 160 mg of LOXO-292 will be coadministered within 30 minutes of the start of a low-fat meal, which will be entirely consumed within 30 minutes. On Days 19-22 and 24-29, omeprazole will be administered following a fast of 2 hours prior to and 1 hour after the omeprazole dose (Note: omeprazole will be administered at approximately the actual time of the Day 12 LOXO-292 dosing).

[l] Primary PK blood samples will be collected prior to dosing (within 30 minutes) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after LOXO-292 administration on Days 1, 12, and 23 for Periods 1, 2, and 3, respectively. The allowed sampling window for PK blood samples will be the following: within 15 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints within the first 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours; and ± 60 minutes for the sampling timepoints ranging from 48 to 168 hours.

[m] Clinical chemistry panel including CK (fasted at least 8 hours), coagulation parameters, complete blood count, and urinalysis will be performed at Screening, Check-in (Day -1), and Days 2, 7, 11 (before ranitidine dosing), 13, 18 (before ranitidine dosing), 22 (before omeprazole dosing), and 24; and at EOT (Day 30) or ET.

[n] Hemoglobin A1c test performed at Screening only.

[o] Alcohol breath test and drugs of abuse urine test, including cotinine. Results from the alcohol and drug tests will be used to determine subject eligibility per the inclusion/exclusion criteria.

[p] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days prior to study drug administration for prescription medications, and 14 days prior to study drug administration for nonprescription medications, will be recorded on the subject's electronic Case Report Form.

[q] Female subjects only.

[r] Postmenopausal female subjects only.

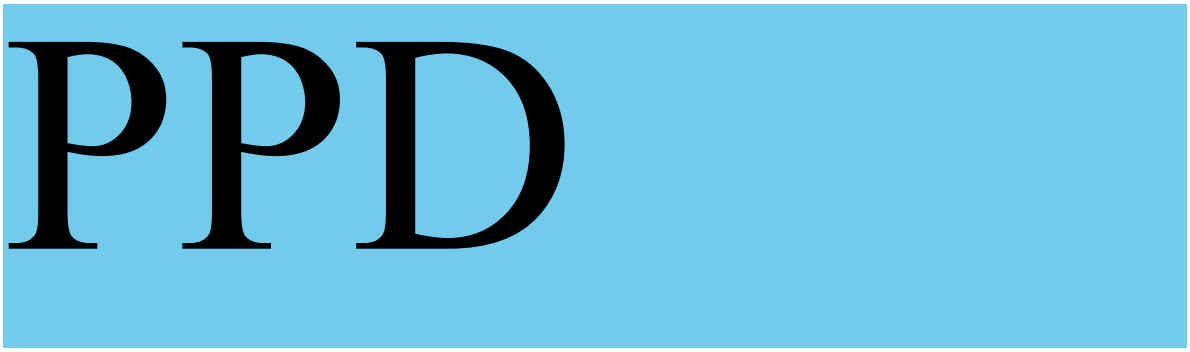
[s] EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 30. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital sign, ECG, and safety laboratory results for serum chemistry, hematology, coagulation, and urinalysis are to be available for review by the Investigator or designee prior to subject release from the CRU at the EOT or ET visit.

[t] To be performed 7 days (± 2 days) following EOT or ET. EOS is defined as when the CRU contacts the subject by a follow-up phone call 7 days (± 2 days) after the EOT visit or ET visit to determine if any SAE or study drug-related AE has occurred since the EOT or ET visit. All subjects who received LOXO-292 (including subjects who are terminated early) will be contacted.

Letter of Administrative Change (LOAC) No. 2
An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Protocol Date: 20 June 2019
Letter of Administrative Change (LOAC) Effective Date: 10 July 2019

Sponsor Reference Number: LOXO-RET-19075
Covance Study Number: 8412-056
IND Number: 133193



Description of Changes:

The purpose of this LOAC is to amend the text in Section 12.1, *Inclusion Criteria*, Sub-Section 12.1.1, *All Subjects* of the Protocol (dated 20 Jun 2019) to include bilateral tubal libgation as an acceptable form of sterilization for female study participants.

Section 12.1, *Inclusion Criteria*, Sub-Section, 12.1.1 *All Subjects* of the Protocol will be revised as follows:

Females of nonchildbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, bilateral oophorectomy, **bilateral tubal ligation** or confirmed tubal occlusion more than 6 months prior to study drug administration) or postmenopausal (defined as at least 12 months postcessation of menses without an alternative medical cause). Postmenopausal status will be confirmed with a screening serum FSH level $\geq$ 40 mIU/mL. All females must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin) at Screening and Check-in (Day -1)

Reason for Changes:

Bilateral tubal libgation was erroneously not listed as an acceptable form of sterilization for female study participants Section 12.1, *Inclusion Criteria*, Sub-Section 12.1.1, *All Subjects*, in the Protocol dated 20 June 2019.

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10-Jul-19 | 13:42:21 PDT

Date

Letter of Administrative Change (LOAC) No. 1
An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Protocol Date: 20 June 2019
Letter of Administrative Change (LOAC) Effective Date: 24 June 2019

Sponsor Reference Number: LOXO-RET-19075
Covance Study Number: 8412-056
IND Number: 133193

Description of Changes:

The purpose of this LOAC is to revise the name of the manufacturer of ranitidine included in Table 2 of Section 5.1, *Description, Storage, Packaging, and Labeling*, of the Protocol, dated 20 Jun 2019.

Table 2 of Section 5.1, *Description, Storage, Packaging, and Labeling* will be revised as follows:

Table 1 Study Drug – Period 2

Study Drug	LOXO-292	Ranitidine
Form	Capsule[a]	Tablet
Strength	80 mg	150 mg
Supplier	Loxo Oncology, Inc.	Covance
Manufacturer	Avista Pharma Solutions, Inc.	Amneal Pharmaceuticals, LLC.

[a]Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.

Reason for Changes:

Table 2 of Section 5.1, *Description, Storage, Packaging, and Labeling* lists the manufacturer of ranitidine 150 mg tablets as Ajanta Pharma Limited. The manufacturer of ranitidine 150 mg tablets to be used in this study is Amneal Pharmaceuticals, LLC.

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24-Jun-19 | 09:45:53 PDT

Date