Protocol: LOXO-BTK-20014 Version 2.0

A Phase 1, Open Label, Randomized, 2-Way Crossover, 3-Period Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

NCT05134350

Approval Date: 29-Jan-2020

Protocol

A Phase 1, Open-label, Randomized, 2-Way Crossover, 3-Period Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

Protocol Status: Final
Protocol Date: 29 January 2020
Protocol Version: 2.0

Investigational Medicinal Product: LOXO-305

Protocol Reference Number: LOXO-BTK-20014
Covance Study Number: 8422329
IND Number: 139876

Sponsor:
Loxo Oncology, Inc.
A wholly owned subsidiary of Eli Lilly and Company
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080
USA

Study Site:
Covance Clinical Research Unit Inc.
1900 Mason Avenue, Suite 140
Daytona Beach, FL 32117
USA

SPONSOR APPROVAL

I have read the protocol and approve it:

PPD

29-Jan-20 | 09:02:54 PST

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PPD

STUDY IDENTIFICATION

Sponsor	Loxo Oncology, Inc. A wholly owned subsidiary of Eli Lilly and Company 701 Gateway Boulevard, Suite 420 South San Francisco, California 94080 USA PPD
Sponsor's Study Contact	PPD Loxo Oncology, Inc. PPD
Sponsor's Medical Contact	PPD Consulting to Loxo Oncology, Inc. PPD
Serious adverse event (SAE) reporting	Email: SAEIntake@Covance.com
Study Site	Covance Clinical Research Unit (CRU), Inc. 1900 Mason Avenue, Suite 140 Daytona Beach, FL 32117 USA PPD
Principal Investigator	PPD Medical Director Covance Clinical Research Unit Inc. 1900 Mason Avenue, Suite 140 Daytona Beach, FL 32117 USA PPD
Sub-investigator(s)	Obtain information from Form FDA 1572
Clinical Laboratories	LabCorp - Hollywood 4200 North 29th Avenue Hollywood, FL 33020 USA
Bioanalytical Laboratory	Alturas Analytics, Inc. 1324 Alturas Drive Moscow, Idaho 83843 USA PPD

Statistician	PPD Covance PPD
Medical Writer	PPD Covance PPD

SYNOPSIS

Study Title

A Phase 1, Open-label, Randomized, 2-Way Crossover, 3-Period Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

Objectives

The primary objectives of the study are:

- to assess the effect of food on the pharmacokinetics (PK) of LOXO-305 administered under fasted conditions and after a standard meal in healthy adult subjects
- to assess the effect of a gastric pH change on the PK of LOXO-305 after multiple-doses of a proton pump inhibitor (PPI; omeprazole) in healthy adult subjects

The secondary objective of the study is:

- to determine the safety and tolerability of a single dose of LOXO-305 administered with and without food and in the presence of a PPI (omeprazole) in healthy adult subjects

Study Design

This is a Phase 1, open-label, randomized, 2-way crossover, 3-period study. A single oral dose of LOXO-305 will be administered under fasted conditions (Treatment A) and fed conditions (Treatment B). Multiple oral doses of omeprazole will be administered once daily from Day 15 through Day 18, with a single oral dose of LOXO-305 co-administered with omeprazole under fasting conditions on Day 18 (Treatment C). PK sampling will be obtained for 168 hours after administration of each dose of LOXO-305 (ie, on Days 1, 8, and 18). The 2 treatment sequences will be ABC and BAC. Subjects will be randomly assigned to 1 of the 2 treatment sequences, according to the randomization scheme issued by Covance.

In Treatment A, a single oral dose of 200 mg LOXO-305 will be administered in the morning on Day 1 or Day 8, following a fast of at least 10 hours prior to and 4 hours after dosing. In Treatment B, a single oral dose of 200 mg LOXO-305 will be administered in the morning on the Day 1 or Day 8, approximately 30 minutes after starting a standard breakfast. In Treatment C, a single oral dose of 40 mg omeprazole will be administered in the morning on Days 15, 16 and 17, following a fast of at least 8 hours prior to omeprazole dosing, followed by a standard breakfast administered approximately 1 hour after dosing. On Day 18, a single oral dose of 40 mg omeprazole will be co-administered with a single oral dose of 200 mg LOXO-305 in the morning, following a fast of at least 10 hours prior to and 4 hours after omeprazole and LOXO-305 co-administration. All standard breakfasts should be entirely consumed within 30 minutes.

Following administration of LOXO-305 in each treatment, blood samples for PK analysis of LOXO-305 will be taken up to 168 hours postdose.

There will be a washout period of 7 days between the doses of LOXO-305 administered in Treatments A and B, and a washout period of 7 days between the doses of LOXO-305 administered in Treatments A or B and the first dose of omeprazole in Treatment C.

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 25, following 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.

In this study, physical examinations, 12-lead electrocardiograms (ECGs), vital signs, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, CK, complete blood count (CBC), 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. Adverse events 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

CCI [redacted] This is a phase 1 study and the sample size is not based upon any formal power calculations but is consistent with previous studies of a similar design.

CCI [redacted]

If subjects are withdrawn by the Investigator (or designee) or voluntarily withdraw prematurely from the study, replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Main Criteria for Inclusion

Male subjects, and female subjects of non-childbearing potential, between 18 and 55 years of age, inclusive, at Screening, and within body mass index (BMI) range 18.0 to 32.0 kg/m^2, inclusive. Subjects will be in good general health, based on medical history, physical examination findings, vital signs, 12-lead electrocardiogram (ECG), or clinical laboratory tests at Screening and/or Check-in (Day -1), as determined by the Investigator (or designee).

Investigational Medicinal Product, Dose, and Mode of Administration

LOXO-305 will be supplied by the Sponsor as 100-mg tablets for oral administration.

Omeprazole will be supplied by Covance as 40-mg capsules for oral administration.

Treatment A (Fasted):

- Day 1 or Day 8 (Treatment A): single oral dose of 200 mg LOXO-305 (2 × 100-mg tablets) following a fast of at least 10 hours prior to and 4 hours after the LOXO-305 dose.

Treatment B (Fed):

- Day 1 or Day 8 (Treatment B): single oral dose of 200 mg LOXO-305 (2 × 100-mg tablets) approximately 30 minutes after starting a standard breakfast. The standard breakfast should be entirely consumed within 30 minutes.

Treatment C (Fasted):

- Days 15, 16, and 17 (Treatment C): single oral dose of 40 mg omeprazole (1 × 40-mg capsule) in the morning following a fast of at least 8 hours prior to the omeprazole dose, followed by a standard breakfast administered approximately 1 hour after dosing. The standard breakfasts should be entirely consumed within 30 minutes.
- Day 18 (Treatment C): single oral dose of 40 mg omeprazole (1 × 40-mg capsule) co-administered with a single oral dose of 200 mg LOXO-305 (2 × 100-mg tablets), following a fast of at least 10 hours prior to and 4 hours after dosing.

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

There will be a washout period of 7 days between the doses of LOXO-305 administered in Treatments A and B, and a washout period of 7 days between the doses of LOXO-305 administered in Treatments A or B and the first dose of omeprazole in Treatment C.

Duration of Subject Participation in the Study:

Planned Study Conduct Duration: up to 63 days.

Screening Period:

Planned Enrollment/Screening Duration: up to 28 days (Day -29 to Day -2).

Length of Confinement:

A total of 26 days (25 nights), from the time of Check-in (Day -1) through 168-hour postdose PK blood draw for Treatment C and EOT assessments (Day 25).

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

Criteria for Evaluation:

Pharmacokinetics:

Serial PK blood samples for the analysis of plasma concentrations of LOXO-305 will be collected from predose through 168 hours post-LOXO-305 administration for each treatment.

The following PK parameters will be calculated, whenever possible, based on the plasma concentrations of LOXO-305 (as appropriate): area under the concentration-time curve from Hour 0 to 24 hours postdose, as calculated by the linear trapezoidal method (AUC_{0-24}), 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-inf}), extrapolation for area under the concentration-time curve ($\%AUC_{extrap}$), maximum observed plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), apparent terminal elimination rate constant (λ_Z), apparent systemic clearance (CL/F). The parameter will be calculated by linear least squares regression analysis using the maximum number of points in the terminal log linear phase (eg, 3 or more non-zero plasma concentrations), and apparent terminal elimination half-life ($t_{½}$).

No value for AUC_{0-inf}, CL/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive timepoints with quantifiable concentrations.

Individual and mean plasma concentration-time curves (both linear and log linear) will be included in the final report.

Safety:

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

Statistical Methods

Pharmacokinetics:

A mixed effect model including planned treatment sequence, period, and actual treatment as fixed effects and subject within planned treatment sequence as a random effect will be used to analyze the natural log (ln)-transformed PK parameters (AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, and C_{max}) and will include calculation of least squared (LS) means and the difference between treatment LS means, as well as their corresponding 90% confidence intervals (CIs). The geometric means ratios (GMR) and their 90% confidence intervals (CIs) of the PK parameter for each treatment comparison will be constructed using the exponentiation of the difference

and the CIs from the mixed effect model. The treatment comparisons of interest include Treatment A versus Treatment B and Treatment A versus Treatment C.

Safety:

All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory results, physical examination results, concomitant medications, and 12-lead ECGs, will be tabulated and summarized, where possible, using descriptive methodology, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of LOXO-305 in each treatment period. No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{extrap}$	extrapolation for area under the concentration-time curve
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from Hour 0 to 24 hours postdose
AUC_{0-inf}	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
BMI	body mass index
BP	blood pressure
BTK	Bruton's tyrosine kinase
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval(s)
CK	creatine kinase
CL/F	apparent systemic clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GI	gastrointestinal tract
GMR	geometric means ratios
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus

HDYF?	How Do You Feel?
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
IRB	Institutional Review Board
ICH	International Council for/Conference on Harmonisation
IUD	intrauterine device
LFT	liver function test(s)
Ln	natural log
LS	least squared
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PT	preferred term
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell(s)
SAE	serious adverse event(s)
SAP	Statistical Analysis Plan
SLL	small lymphocytic lymphoma
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time to maximum observed concentration
TSH	thyroid-stimulating hormone
UA	urinalysis
WBC	white blood cell(s)
WHO	World Health Organization
WM	Waldenstrom's macroglobulinemia
λ_Z	apparent terminal elimination rate constant

1. INTRODUCTION

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

1.1. Background

LOXO-305 (also known as LY3527727) is a selective inhibitor of the Bruton's tyrosine kinase (BTK) being developed by Loxo Oncology. In enzyme and cellular assays, LOXO-305 potently inhibits wild-type-BTK and the BTK C481S-acquired resistance mutation which results from a serine substitution at position 481. This inhibitory activity correlated with significant inhibition of growth of BTK-dependent human lymphoma cell lines. C481S mutations (and other substitutions of this cysteine residue) are clinically important because they may explain more than half the cases of acquired resistance to commercially available covalent BTK inhibitors in patients with chronic lymphocytic leukemia (CLL), and have also been identified in Waldenstrom's macroglobulinemia (WM) and mantle cell lymphoma (MCL) patients.[2–5] CCI

Irreversible BTK inhibitors like ibrutinib and acalabrutinib have transformed the treatment landscape of several BTK-dependent B-cell malignancies, including CLL, WM, MCL, and marginal zone lymphoma (MZL). However, the efficacy of these agents in the long term is limited by the development of mutations in BTK, most commonly through BTK C481 substitution mutations that prevent covalent binding and inactivation of BTK by irreversible inhibitors. Additionally, half of patients who discontinue ibrutinib therapy have AEs which are attributed to off-target effects and limit long-term use of ibrutinib. Therefore, a more potent and selective inhibitor of BTK with activity against BTK-wt and C481 mutant BTK may provide clinical benefit to patients with B-cell malignancies where treatment with irreversible BTK inhibitors has failed.

LOXO-305 is a small molecule that was designed to block the adenosine triphosphate (ATP) binding site of the BTK kinase competitively and has single digit nanomolar activity against BTK-wt and C481S. There is no evidence of covalent or irreversible binding. Loxo Oncology is initiating the clinical development of LOXO-305 for the treatment of patients with previously treated CLL/small lymphocytic lymphoma (SLL), WM, MCL, MZL, and other B-cell non-Hodgkin lymphoma (NHL).

1.2. Non-clinical Pharmacokinetics

In non-clinical studies, LOXO-305 was metabolized slowly by human microsomal fractions and hepatocytes. The low rates of metabolism in both these human in vitro systems suggest that LOXO-305 will have low clearance in humans. In vitro data with cloned expressed cytochrome P450 (CYP) enzymes and human liver microsomes indicate that CYP3A4 is the primary enzyme that metabolizes LOXO-305.

There was very little metabolism of LOXO-305 in human hepatocytes and the only metabolite detected was a glucuronide of LOXO-305. The glucuronide formed by the human

hepatocytes was also formed by rat and dog hepatocytes, supporting the use of rat and dog for non-clinical safety assessment.

Renal clearance of LOXO-305 in male and female rats was negligible. No renal clearance data are available in other species, but this pathway is often conserved across species and therefore, no renal clearance is expected in humans.

1.3. Summary of Clinical Experience

LOXO-305 is currently being studied in an ongoing global Phase 1/2 first-in-human study, LOXO-BTK-18001, in patients with previously treated CLL/SLL or NHL. The starting dose of LOXO-305 was 25 mg once daily (QD).

As of 27 September 2019 (data cutoff date), safety data were available from 28 treated patients, with 200 mg QD as the highest dose administered (Section 1.3.1). As of 25 October 2019, Day 8 of Cycle 1 pharmacokinetic (PK) data were available from 25 patients (Section 1.3.2).

1.3.1. Safety

As of 27 September 2019, 27 (96.4%) of the 28 patients were continuing treatment; 1 patient in the 25 mg QD cohort discontinued treatment due to progressive disease and withdrew consent.

Overall, 22 (78.6%) patients experienced at least 1 treatment-emergent AE (TEAE), regardless of relationship to study drug. Treatment-emergent AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Across the 25 mg to 200-mg QD dose range, the most frequently reported TEAEs (> 10% of patients), regardless of relationship to study drug, were fatigue (25.0%), diarrhea (17.9%), anemia (14.3%), arthralgia (10.7%), back pain (10.7%), increased blood bilirubin (10.7%), contusion (10.7%), and maculo-papular rash (10.7%).

As of the data cut off of 27 September 2019, most TEAEs were mild or moderate (Grade 1 or 2) in severity. Grade 3 TEAEs have been reported in 2 patients to date, 1 with neutropenia and 1 with leukocytosis, the latter also reported as a serious AE (SAE). Both of these were assessed by the Investigator as related to the study drug.

1.3.2. Pharmacokinetics

As of 25 October 2019, preliminary steady-state PK data (Day 8 of Cycle 1) were available from 25 patients enrolled in LOXO-BTK-18001. These data demonstrate that LOXO-305 is absorbed after oral administration with a median time to maximum observed concentration (t_{max}) of approximately 2 hours and low clearance (Table 1).

Although the plasma half-life could not be calculated with certainty because of the limited sampling interval (0 to 8 hours), it appears to be approximately 18 hours. Steady-state PK parameters of LOXO-305 in these cancer patients are presented in Table 1. Following administration of the 100 mg QD, 150 mg QD, or 200 mg QD, mean unbound trough plasma levels of LOXO-305 exceeded the concentration required for 90% inhibition (IC_{90}) of the C481S mutant of BTK in vitro.

1.4. Study Rationale

The study is designed to determine the dosing conditions which might affect the PK profile of LOXO-305 in healthy adult subjects.

This study will support assessment of early phase drug combinations of FDA-approved products with LOXO-305 as part of the ongoing clinical trial, LOXO-BTK-18001. For approved products, administration will follow specifications of the United States package insert, which may specify administration with "food", not specifically a "high fat meal". A "standard meal" is considered more consistent with the food conditions identified in the package insert of the approved products that will be assessed in combination with LOXO-305.[6] The effect of food will be assessed by measuring the change in the PK of LOXO-305 after dosing under fed conditions (with a standard breakfast) versus fasting condition. In consideration of the diet which the patient population LOXO-305 is intended to treat (patients with previously treated CLL/SLL, WM, MCL, MZL, and other B-cell NHL) normally consume, a standard breakfast has been chosen as the meal with which to administer LOXO-305 under fed conditions (Treatment B).

The aqueous solubility of LOXO-305 is similar across the range of pH in the gastrointestinal (GI) track CCI and therefore there is unlikely to be an effect of GI pH modification on the solubility and subsequent oral absorption of LOXO-305 from the GI tract. However, LOXO-305 is formulated with excipients that cause release of LOXO-305 from the formulation to be somewhat slower under acidic conditions than neutral conditions, and the clinical impact of this slower dissolution is unknown. The effect of reduced stomach acidity on the PK of LOXO-305 will be tested in this study by raising the gastric pH with omeprazole, a proton pump inhibitor (PPI).

A PPI was selected over other antacids drugs because this drug class is considered to suppress gastric acid secretion to a greater extent and for a longer duration than some other gastric pH-elevating agents, such as H_2 blockers and antacids.

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. The dose of LOXO-305 administered in this study is not anticipated to induce any potential risk to subjects participating in this study as it is a single dose which does not exceed the highest dose safely administered in first in human studies.[1] More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-305 may be found in the IB.[1]

The potential risk of participating in this study is well managed by the study set-up and is considered negligible. The safety monitoring practices employed will include AE reporting, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory evaluations, and physical examinations, and are considered adequate to protect the subjects' safety.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objectives of the study are:

- to assess the effect of food on the PK of LOXO-305 administered under fasted conditions and after a standard meal in healthy adult subjects
- to assess the effect of a gastric pH change on the PK of LOXO-305 after multiple-doses of a PPI (omeprazole) in healthy adult subjects

The secondary objective of the study is:

- to determine the safety and tolerability of a single dose of LOXO-305 administered with and without food and in the presence of a PPI (omeprazole) in healthy adult subjects

2.2. Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-305 (as appropriate):

- area under the concentration-time curve from Hour 0 to 24 hours postdose, as calculated by the linear trapezoidal method (AUC_{0-24})
- 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-inf})
- extrapolation for area under the concentration-time curve ($\%AUC_{extrap}$)
- maximum observed plasma concentration (C_{max})
- time to maximum observed concentration (t_{max})

- apparent terminal elimination rate constant (λ_Z)
- apparent systemic clearance (CL/F)
- apparent terminal elimination half-life ($t_{½}$).

No value for $AUC_{0\text{-inf}}$, CL/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive timepoints with quantifiable concentrations.

Individual and mean plasma concentration-time curves (both linear and log linear) will be included in the final report.

Safety and tolerability will be assessed by monitoring AEs, performing physical examinations and clinical laboratory tests, measuring vital signs, and 12-lead ECGs.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 1, open-label, randomized, 2-way crossover, 3-period study. A single oral dose of LOXO-305 will be administered under fasted conditions (Treatment A) and fed conditions (Treatment B). Multiple oral doses of omeprazole will be administered once daily from Day 15 through Day 18, with a single oral dose of LOXO-305 co-administered with omeprazole under fasted conditions on Day 18 (Treatment C). PK sampling will be obtained for 168 hours after administration of each dose of LOXO-305 (ie, on Days 1, 8, and 18). The 2 treatment sequences will be ABC and BAC. Subjects will be randomly assigned to 1 of the 2 treatment sequences, according to a randomization scheme issued by Covance.

In Treatment A, a single oral dose of 200 mg LOXO-305 will be administered in the morning on Day 1 or Day 8 (according to the randomization scheme), following a fast of at least 10 hours prior to and 4 hours after dosing. In Treatment B, a single oral dose of 200 mg LOXO-305 will be administered in the morning on Day 1 or Day 8 (according to the randomization scheme), approximately 30 minutes after starting a standard breakfast. In Treatment C, a single oral dose of 40 mg omeprazole will be administered in the morning on Days 15, 16 and 17, following a fast of at least 8 hours prior to omeprazole dosing, followed by a standard breakfast administered approximately 1 hour after dosing. On Day 18, a single oral dose of 40 mg omeprazole will be co-administered with a single oral dose of 200 mg LOXO-305 in the morning, following a fast of at least 10 hours prior to and 4 hours after omeprazole and LOXO-305 co-administration. Standard breakfasts should be entirely consumed within 30 minutes. Serial PK blood samples for the analysis of plasma concentrations of LOXO-305 will be collected from predose through 168 hours postdose for each treatment.

There will be a washout period of 7 days between the doses of LOXO-305 administered in Treatments A and B, and a washout period of 7 days between the doses of LOXO-305 administered in Treatments A or B and the first dose of omeprazole in Treatment C.

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 25 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, physical examinations, 12-lead ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, creatine kinase (CK), complete blood count (CBC), 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). Adverse events and SAEs will be collected beginning at informed consent. Adverse events 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. Study completion is defined as the time of the last subject's follow-up phone call.

3.2. Discussion of Study Design

Overall

The study is designed to determine the dosing conditions which might affect the PK profile of LOXO-305 in healthy adult subjects.

The effect of food will be thus assessed by measuring the change in the PK of LOXO-305 after dosing under fed conditions (with a standard breakfast) versus fasting condition. This study will support assessment of early phase drug combinations of FDA-approved products with LOXO-305 as part of the ongoing clinical trial, LOXO-BTK-18001. For approved products, administration will follow specifications of the United States product insert, which may specify administration with "food", not specifically a "high fat meal". A "standard meal" is considered more consistent with the food conditions identified in the package insert of the approved products that will be assessed in combination with LOXO-305. In consideration of the diet which the patient population LOXO-305 is intended to treat (patients with previously treated CLL/SLL, WM, MCL, MZL, and other B-cell NHL) normally consume, a standard

breakfast has been chosen as the meal with which to administer LOXO-305 under fed conditions (Treatment B).[6]

The aqueous solubility of LOXO-305 is similar across the range of pH in the GI track (e.g. CCI Loxo Oncology Inc., data on file) and therefore there is unlikely to be an effect of GI pH modification on the solubility and subsequent oral absorption of LOXO-305 from the GI tract. However, LOXO-305 is formulated with excipients that cause release of LOXO-305 from the formulation to be somewhat slower under acidic conditions than neutral conditions, and the clinical impact of this slower dissolution is unknown. The effect of reduced stomach acidity on the PK of LOXO-305 will be tested in this study by raising the gastric pH with omeprazole, a PPI.

A PPI was selected over other antacids drugs because this drug class is considered to suppress gastric acid secretion to a greater extent and for a longer duration than some other gastric pH-elevating agents, such as H_2 blockers and antacids.

Subjects will be randomized to treatment sequences to minimize assignment bias. The 2 treatment sequences will be ABC and BAC. Subjects will be randomly assigned to 1 of the 2 treatment sequences, according to the randomization scheme issued by Covance. A crossover design is used to reduce the residual variability as every subject acts as their own control. The washout period of 7 days between LOXO-305 doses in Treatments A and B and the washout period of 7 days between the doses of LOXO-305 administered in Treatments A or B and the first dose of omeprazole in Treatment C is considered sufficient to prevent carryover effects of the treatments.

Conducting the study in healthy adult subjects mitigates the potential confounding effects of the disease state and concomitant medications.

3.3. Selection of Doses in the Study

3.3.1. LOXO-305

Single oral doses of 200 mg LOXO-305 will be evaluated as this is the anticipated therapeutic dose level. Doses of LOXO-305 from 25 mg QD to 200 mg QD have been evaluated in a Phase 1/2 first-in-human study in patients with previously treated CLL/SLL or NHL with ongoing dose escalation above 200 mg QD as approved by the study's Safety Review Committee. The available data demonstrate that LOXO-305 appears safe and well tolerated at these doses. At all evaluated doses, including doses above 200 mg QD, no dose-limiting toxicities have been identified in humans.[1]

3.3.2. Omeprazole

A dose of 40 mg omeprazole once daily is within the recommended dose as prescribed in the labeling.[7] In addition, multiple doses for 4 consecutive days 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.

4. SELECTION OF STUDY 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. Inclusion/exclusion criteria
2. Informed consent
3. Demographic data
4. Medical history (including review of medication[s])
5. Height, weight, and body mass index (BMI)
6. Complete physical examination (Section 7.2.5)
7. 12-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 blood pressure [BP] and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
9. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
10. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CK, CBC, and UA; Appendix 2)
11. Screens for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), and human immunodeficiency virus (HIV) antibody (Appendix 2)
12. Hemoglobin A1c (HbA1c) test (Appendix 2)
13. Screen for selected drugs of abuse, including cotinine and an alcohol breath test (Appendix 2)
14. Serum pregnancy test (for female subjects only; Appendix 2)
15. Follicle-stimulating hormone (FSH) test (for post-menopausal female subjects only; Appendix 2)
16. Thyroid-stimulating hormone (TSH) test (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. Review of inclusion/exclusion criteria
2. Interim medical history, including concomitant medication(s)
3. Weight and BMI
4. Abbreviated physical examination (Section 7.2.5)

5. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
6. Vital signs (including oral temperature, respiratory rate, and supine BP and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
7. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
8. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CK, CBC, and UA; Appendix 2)
9. Screen for selected drugs of abuse, including cotinine and an alcohol breath test (Appendix 2)
10. Serum pregnancy test (for female subjects only; Appendix 2)
11. 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; #1, Section 4.2). 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 non-childbearing potential, between 18 and 55 years of age, inclusive, at Screening.
2. Within BMI range 18.0 to 32.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, or clinical laboratory evaluations (Appendix 4) at Screening and/or Check-in (Day -1) as assessed by the Investigator (or designee).
4. Female subjects of non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to study drug administration) or post-menopausal (defined as at least 12 months post-cessation of menses without an alternative medical cause). Post-menopausal status will be confirmed with a screening serum FSH level ≥ 40 mIU/mL. All female subjects must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin, serum quantitative human chorionic gonadotropin tests may be used for confirmation as needed) at Screening and Check-in (Day -1).

5. Male subjects who are capable of fathering a child must agree to use 1 of the following methods of contraception from the time of the dose administration through 6 months after the last dose of LOXO-305 administration:

    a. 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 1 of the contraception methods below:

        i. Male condom with spermicide, or

        ii. A male subject must ensure that their female partner meets 1 of the following criteria:

            1. intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);

            2. established use of oral, implanted, transdermal, intravaginal, or hormonal method of contraception associated with inhibition of ovulation; or

            3. bilateral tubal ligation or,

            4. be postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status.

    Male subjects 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, post-ovulation 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 25-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:

    i. liver disease

    ii. pancreatitis

iii. peptic ulcer disease

iv. intestinal malabsorption

v. gastric reduction surgery

vi. history or presence of clinically significant cardiovascular disease:

vii. Myocardial infarction or cerebrovascular thromboembolism within 6 months prior to the first dose administration (Day 1)

viii. Symptomatic angina pectoris within 6 months prior to the first dose administration (Day 1)

ix. New York Heart Association Class ≥ 2 congestive heart failure within 6 months prior to the first dose administration (Day 1)

x. Congenital prolonged QT syndrome

xi. Ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)

xii. Arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention

xiii. Ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)

xiv. 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:

i. oral body temperature > 37.5°C;

ii. pulse rate < 50 or > 99 beats per minute (bpm);

iii. systolic BP < 89 or > 139 mmHg;

iv. 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 pulse rate 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 pulse rate 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 physical examination at Screening and/or Check-in (Day -1).
5. Abnormal liver function tests (LFTs), as defined by aspartate aminotransferase (AST), alanine aminotransferase (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 (Day -1). 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 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
8. Positive serologic test for HBsAg, HCV, or HIV antibody at Screening.
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). Alcohol breath tests must be negative at both Screening and 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) and Sponsor.
12. Positive urine screen for drugs of abuse at Screening or Check-in (Day -1).
13. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET.
14. History of significant hypersensitivity, intolerance, or allergy to any drug compound (including omeprazole), food, or other substance, unless approved by the Investigator (or designee).
15. 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).
16. Use or intention to use any prescription or over-the-counter medications (including but not limited to any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers, strong P-glycoprotein (P-gp) inhibitors, PPIs [with the exception of omeprazole administered for the purposes of this study/in accordance with the Protocol], antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, herbal products, natural or herbal supplements, and hormone-replacement therapy [HRT]) 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.
17. History of a major surgical procedure within 30 days prior to Screening.

18. 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.
19. 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-305.
20. Poor peripheral venous access.
21. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
22. Receipt of blood products within 2 months prior to Check-in (Day -1).
23. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET.
24. 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).
Note: subjects with a history of uncomplicated cholecystectomy, appendectomy and/or hernia repairs will be acceptable.
25. History of diabetes mellitus; HbA1c $\geq$ 6.5%.
26. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).
27. Have previously completed or withdrawn from any other study investigating LOXO-305 and have previously received the investigational product.
28. 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.
29. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

4.5. Subject Number and Identification

Subject numbers 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). If subjects are withdrawn by the Investigator (or designee) or voluntarily withdraw prematurely from the study, replacement subjects may 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 non-permitted 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 EOS 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 (Table 2).

Table 2: Study Drug

Study Drug	LOXO-305	Omeprazole
Form	Tablet	Capsule
Strength	100 mg	40 mg
Supplier	Loxo Oncology, Inc.	Covance
Manufacturer	Catalent San Diego or Lonza Pharma & Biotech	Sandoz, Inc.

Note: for LOXO-305, specific manufacturer and purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.

The tablets containing 100 mg LOXO-305 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.

The capsules containing 40 mg of omeprazole will be supplied by the site, along with the lot numbers. Omeprazole 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

In Treatment A, a single oral dose of 200 mg LOXO-305 will be administered in the morning on Day 1 or Day 8, following a fast of at least 10 hours prior to and 4 hours after dosing.

In Treatment B, a single oral dose of 200 mg LOXO-305 will be administered in the morning on Day 1 or Day 8, approximately 30 minutes after starting a standard breakfast. Standard breakfasts should be entirely consumed within 30 minutes.

In Treatment C, a single oral dose of 40 mg omeprazole will be administered in the morning on Days 15, 16 and 17, following a fast of at least 8 hours prior to omeprazole dosing, followed by a standard breakfast administered approximately 1 hour after dosing. On Day 18, a single oral dose of 40 mg omeprazole will be co-administered with a single oral dose of 200 mg LOXO-305 in the morning, following a fast of at least 10 hours prior to and 4 hours after omeprazole and LOXO-305 co-administration. 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 CRU staff. Each unit dose container will be appropriately labeled.

Appropriate unit dose(s), as described above, will be administered to 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 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-305 dose administration, except as necessitated by the occurrence of an AE(s) and/or study procedure(s).

5.3. Randomization

Subjects will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number (in accordance with the requirements in Section 4.5 and the randomization scheme generated by Covance) prior to the time of the first dose, different from the screening number, and will receive the corresponding product according to the randomization scheme generated by Covance.

Subjects will receive each treatment (A, B, and C) on one occasion. The treatments will be administered on Days 1 (Treatment A or B), 8 (Treatment A or B), and Days 15-18 (Treatment C). The sequences to be used in the randomization will be ABC and BAC.

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, a visual inspection of the mouth and hands will be performed for each subject.
- At each dose preparation occasion, a predose and postdose inventory of LOXO-305 and omeprazole (as appropriate) will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of LOXO-305 tablets and omeprazole capsules 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-305 tablets and omeprazole capsules will be disposed of by the CRU, following the Sponsor’s written/emailed instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Paracetamol/acetaminophen (maximum of 2 g/day for up to 3 consecutive days) is an acceptable concomitant medication.

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the EOT or ET, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

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 first dose administration (Day 1).

All prescription and over-the-counter medications (including HRT, herbal products, natural or herbal supplements, except for paracetamol/acetaminophen as referenced above) 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, PPIs [with the exception of omeprazole administered for the purposes of this study/in accordance with the Protocol], antacids, H_2-receptor antagonists, 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, should not begin a new exercise program or participate in any unusually strenuous physical exertion).

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

Dietary requirement in relation to dosing are described in Section 3.1 and Section 5.2.

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-305 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 samples will be provided in a separate Laboratory Manual. The number of blood samples and total blood volume required for PK testing is presented in Appendix 3.

7.1.2. Analytical Methodology

Concentrations of LOXO-305 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
- PK blood sampling
- vital signs assessments
- 12-lead ECGs
- blood and urine samples for clinical laboratories
- physical examination.

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 non-leading 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.

Adverse events, whether volunteered, identified by the subject's responses to HDYF? inquiries, or noted on physical examination, 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 SAE or drug-related 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 suspected unexpected serious adverse reaction (SUSAR) will be reported to the Institutional Review Board (IRB) 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-305 for expected adverse reactions.

7.2.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations (clinical chemistry panel [fasted at least 8 hours], coagulation parameters, CK, CBC, TSH [Screening only], HbA1c [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 (female subjects only [serum quantitative may be used for confirmation if needed]) and an FSH test (post-menopausal female subjects 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 evaluations is in Appendix 2.

7.2.3. Vital Signs

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

Blood pressure and pulse rate 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 heart rate 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 physical examination will be performed at the timepoints specified in Appendix 4. Complete physical examinations 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 physical examinations 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] This is a phase 1 study and the sample size is not based upon any formal power calculations but is consistent with previous studies of a similar design.

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-305, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration.

The **Safety Population** will consist of all subjects who have received at least 1 dose of LOXO-305. Subjects will be classified into groups based on actual treatment received.

8.3. Pharmacokinetic Analysis

Serial PK blood samples for the analysis of plasma concentrations of LOXO-305 will be collected from predose through 168 hours post-LOXO-305 dose for each treatment.

Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of LOXO-305 (as appropriate):

$AUC_{0\text{-}24}$	area under the concentration-time curve from Hour 0 to 24 hours postdose, as calculated by the linear trapezoidal method
$AUC_{0\text{-}t}$	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
$AUC_{0\text{-}inf}$	AUC extrapolated to infinity, calculated using the formula: $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + \frac{C_t}{\lambda_z}$ 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 plasma 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 $t_{½} = \ln(2)/\lambda_Z$

Pharmacokinetic calculations will be performed using commercial software such as Phoenix™ WinNonlin® Version 8.1 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. Statistical Methodology

The primary PK analysis planned for this study is a mixed effect model including planned treatment sequence, period, and actual treatment as fixed effects and subject within planned treatment sequence as a random effect will be used to analyze the natural log (ln)-transformed PK parameters (AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, and C_{max}) and will include calculation of least squared (LS) means and the difference between treatment LS means, as well as their corresponding 90% confidence intervals (CIs). The geometric mean ratios (GMR) and their 90% CIs of the PK parameter for each treatment comparison will be constructed using the exponentiation of the difference and the CIs from the mixed effect model.

The comparisons of interest are as follows:

- Treatment A compared with Treatment B
- Treatment A compared with Treatment C

8.4. Safety Analysis

All safety assessments, including AEs and SAEs, vital signs measurements, clinical laboratory results, physical examination results, concomitant medications, and 12-lead ECGs, will be tabulated and summarized, where possible, using descriptive methodology, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of LOXO-305 in each treatment 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 (WHO Drug 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 (Appendix 1 for AE reporting). All TEAEs will be summarized by SOC and PT, using 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 CRU staff to familiarize the Investigator (or designee) and CRU 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 (ICH) Guidelines, are commonly known as Good Clinical Practices (GCP), 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-305 – Investigator's Brochure (Version 2). 18 November 2019.

2. Chiron D, Di Liberto M, Martin P, Huang X, Sharman J, Blecua P, et al. Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma. Cancer Discov. 2014 Sep;4(9):1022–35.

3. Woyach JA, Furman RR, Liu T-M, Ozer HG, Zapatka M, Ruppert AS, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med. 2014 Jun 12;370(24):2286–94.

4. Woyach JA, Ruppert AS, Guinn D, Lehman A, Blachly JS, Lozanski A, et al. BTKC481S-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. J Clin Oncol. 2017 May 1;35(13):1437–43.

5. Xu L, Tsakmaklis N, Yang G, Chen JG, Liu X, Demos M, et al. Acquired mutations associated with ibrutinib resistance in Waldenström macroglobulinemia. Blood. 2017 04;129(18):2519–25.

6. Food and Drug Administration. Guidance for Industry, Draft Guidance: Assessing the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations [Internet]. Food and Drug Administration; 2019. Available from: https://www.fda.gov/media/121313/download

7. Sandoz Inc. OMEPRAZOLE - omeprazole capsule, delayed release (HIGHLIGHTS OF PRESCRIBING INFORMATION). 2018.

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 adult subject, whether or not considered drug-related by the Investigator (or designee). A treatment-emergent adverse event (TEAE) 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:** An event that puts the subject at immediate risk of death
- **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 email to Covance or the Sponsor's Clinical Safety Representative within 24 hours of being notified. Covance or the Sponsor's Clinical Safety Representative will then forward the Pregnancy Form to the Investigator for completion.

email: SAEIntake@Covance.com

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and ET 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 Covance or 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 adverse event (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 Covance or the Sponsor's Clinical Safety Representative via email.

All pregnancies should be recorded on the AE electronic eCRF (as appropriate), 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 Food and Drug Administration [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 Investigator’s Brochure (IB) or if it is not listed at the specificity or severity that has been observed for an unapproved investigational medicinal product (IMP).

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 suspected unexpected serious adverse reaction (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, Covance or the Sponsor’s Clinical Safety Representative will be notified by the Investigator or designee in writing using the following email address:

email: SAEIntake@Covance.com

To report the SAE, the completed report form should be sent by email to Covance or 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):	Complete Blood Count (CBC):	Other Tests:
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Amylase Aspartate aminotransferase (AST) Bilirubin (direct and total) Blood urea nitrogen Calcium Chloride Cholesterol Creatine kinase (CK) Creatinine Glucose Iron Lipase Magnesium Phosphorus Potassium Sodium Total protein Triglycerides Uric acid	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	Hemoglobin A1c (HbA1c)[b] Thyroid-stimulating hormone (TSH)[b]
		Coagulation Parameters:
		Activated partial thrombin time Partial thromboplastin time Prothrombin time International normalized ratio
		Serology:[b]
		Human immunodeficiency virus (HIV) antibody Hepatitis B surface antigen (HBsAg) Hepatitis C virus (HCV) antibody
		For Female Subjects only:
		Pregnancy test (serum qualitative, serum quantitative may be used for confirmation if needed)[c] Follicle-stimulating hormone (post-menopausal female subjects only)[b]
Urine Drug Screen:[a]	**Urinalysis:**	Estimated creatinine clearance[a]
Including but not limited to the following: Alcohol (ethanol) (breath test) Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine (metabolite) Methadone Opiates Phencyclidine Cotinine	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)	

a. Performed at Screening and Check-in (Day -1) only.
b. Performed at Screening only.
c. Performed at Screening, Check-in (Day -1), and End of Treatment (EOT)/Early Termination (ET) only.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject participating in this study:

Assessment	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	CCI		
Hemoglobin A1c (HbA1c)			
Primary pharmacokinetic (PK) sampling			
Clinical laboratory tests: Complete blood count (CBC) Clinical chemistry panel Coagulation parameters			
Serum pregnancy test (female subjects only)			
Serum follicle-stimulating hormone (FSH; post-menopausal female subjects only)			
Thyroid-stimulating hormone (TSH)			

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 400 mL.

Appendix 4: Schedule of Assessments

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Study Days 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Clinic Discharge/ EOT (Day 25) or ET[v]	Follow-up Phone Call (EOS) 7 (±2) days post EOT or ET[w]
Confined to the CRU		X	X	X	X	X	X	X	X	X	X	X	X	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	
12-lead ECG[e]	X	X	X			X				X			X				X			X			X				X	
Vital Signs[f]	X[g]	X[g]	X	X		X				X	X		X				X			X			X				X[g]	
HDYF? Inquiry[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LOXO-305 Dosing			X[j]							X[k]										X[m]								
Omeprazole Dosing																	X[l]	X[l]	X[l]	X[m]								
CCI																												
Clinical Laboratory Evaluations[p]	X	X				X			X				X						X				X				X	
Hepatitis and HIV Screen	X																											
HbA1c Test[q]	X																											
Drug Screen[r]	X	X																										

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Study Days																								Clinic Discharge/ EOT (Day 25) or ET[v]	Follow -up Phone Call (EOS)
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		7 (±2) days post EOT or ET[w]
Prior and Concomitant Medications[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[t]	X	X																									X	
FSH Test[u]	X																											
TSH Test	X																											

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; CBC = complete blood count; CK = creatine kinase; CRU = Clinical Research Unit; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; ICF = Informed Consent Form; PK = pharmacokinetic; SAE = serious adverse event; TSH = thyroid-stimulating hormone; UA = urinalysis.

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 physical examination will be performed at Screening. An abbreviated physical examination will be performed at Check-in (Day -1) and at EOT (Day 25).
e. 12-lead ECGs 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 (predose and 2 hours after LOXO-305 dosing), Day 4 (ie, 72 hours after LOXO-305 dosing on Day 1), Day 8 (predose), Day 11 (ie, 72 hours after LOXO-305 dosing on Day 8), Day 15 (predose), Day 18 (predose), Day 21 (ie, 72 hours after LOXO-305 dosing on Day 18), and at EOT/Day 25 (168 hours after LOXO-305 dosing on Day 18) or ET.
f. Vital signs measurements (supine BP and pulse rate) will be obtained at Screening and Day -1, Day 1 (predose and 2, 4, 8, and 12 hours after LOXO-305 dosing), Day 2 (ie 24 hours after LOXO-305 dosing on Day 1), Day 4 (ie, 72 hours after LOXO-305 dosing on Day 1), Day 8 (predose and 2, 4, 8, and 12 hours after LOXO-305 dosing [on Day 8]), Day 9 (ie 24 hours after LOXO-305 dosing on Day 8), Day 11 (ie, 72 hours after LOXO-305 dosing on Day 8), Day 15 (predose), Day 18 (predose and 2 hours after LOXO-305 dosing on Day 18), Day 21 (ie, 72 hours after LOXO-305 dosing on Day 18), and at EOT/Day 25 (168 hours after LOXO-305 dosing on Day 18) or ET. Vital signs measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.
g. Oral temperature and respiratory rate will also be obtained at at Screening, Day -1, and at EOT/Day 25 (168 hours after LOXO-305 dosing on Day 18) or ET.
h. An HDYF? inquiry will be 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.
i. Adverse events and SAEs will be collected beginning at informed consent. Adverse events 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.

j. On Day 1, LOXO-305 will be administered in the morning, either following a fast of at least 10 hours prior to and 4 hours after the LOXO-305 dose or approximately 30 minutes after the start of a standard breakfast, according to the treatment sequence the subject is randomly assigned to. Standard breakfast should be entirely consumed within 30 minutes.
k. On Day 8, LOXO-305 will be administered in the morning, either following a fast of at least 10 hours prior to and 4 hours after the LOXO-305 dose or approximately 30 minutes after the start of a standard breakfast, according to the treatment sequence the subject is randomly assigned to. Standard breakfast should be entirely consumed within 30 minutes.
l. On Days 15, 16, and 17 omeprazole will be administered in the morning following a fast of at least 8 hours prior to the omeprazole dose, followed by a standard breakfast administered approximately 1 hour after dosing. Standard breakfast should be entirely consumed within 30 minutes.
m. On Day 18, LOXO-305 and omeprazole will be co-administered in the morning, following a fast of at least 10 hours prior to and 4 hours after the omeprazole and LOXO-305 co-administration.

CCI [redacted]

p. Clinical chemistry panel including CK (fasted at least 8 hours), coagulation parameters, CBC, and UA will be performed at Screening, Check-in (Day -1), Days 4, 7, 11, 17, 21, and at EOT (Day 25) or ET.
q. Hemoglobin A1c test performed at Screening only.
r. 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.
s. 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 non-prescription medications, will be recorded on the subject's electronic Case Report Form.
t. Female subjects only.
u. Post-menopausal female subjects only.
v. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 25. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital signs, ECG, and safety laboratory results for clinical chemistry, hematology, coagulation, and UA are to be available for review by the Investigator or designee prior to subject release from the CRU at the EOT or ET visit.
w. 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-305 (including subjects who are terminated early) will be contacted.

Appendix 5: Protocol Amendment Summary of Changes

Protocol Version 2.0 (dated 29th January 2020) incorporated the following changes in Protocol Version 1.0 (dated 14th January 2020):

- The study duration has been extended to include an additional treatment (Treatment C) to assess the effect of a gastric pH change on the pharmacokinetics (PK) of LOXO-305 after multiple-doses of a proton pump inhibitor (PPI; omeprazole). The following changes were made:
    - The duration of confinement in the Clinical Research Unit has been extended from 16 days (Day -1 to Day 15) to 26 days (Day -1 to Day 25).
    - Clinic Discharge/End of Treatment (EOT) assessments that were conducted on Day 15 will now be conducted on Day 25.
    - Early Termination (ET) assessments that were conducted as per the assessments on Day 15 will now be conducted as per the assessments on Day 25.
    - All subjects will be administered a dose of 40 mg omeprazole once daily from Day 15 through Day 18, with a single oral dose of 200 mg LOXO-305 co-administered with omeprazole on Day 18 (Treatment C).
    - The treatment sequences AB and BA to be used in the randomization have been updated to ABC and BAC.
    - On Day 15 to Day 17, single oral doses of 40 mg omeprazole will be administered following a fast of at least 8 hours prior to dosing, followed by a standard breakfast administered approximately 1 hour after dosing. On Day 18, a single oral dose of 40 mg omeprazole will be co-administered with a single oral dose of 200 mg LOXO-305 in the morning, following a fast of at least 10 hours prior to and 4 hours after dosing omeprazole and LOXO-305 co-administration.
    - There will be a washout period of 7 days between dosing of LOXO-305 on Day 8 and the first dose of omeprazole on Day 15.

CCI [redacted]

    - Additional safety monitoring assessments will be conducted as follows:
        - Concomitant medication, adverse event, and serious adverse event monitoring, and How do you feel? Inquiry will be conducted on Day 15 through Day 25.
        - Vital signs (blood pressure and pulse rate) and electrocardiogram assessments will be conducted at Day 15 (predose), Day 18 (predose and 2 hours after LOXO-305 dosing on Day 18), and Day 21 (ie, 72 hours after LOXO-305 dosing on Day 18).
        - Clinical laboratory evaluations will be conducted on Day 17 and Day 21.

- Rationale for the amended study design and selection of omeprazole dose has been included.

LOXO-305 is formulated with excipients that cause release of LOXO-305 from the formulation to be somewhat slower under acidic conditions than neutral conditions, and the clinical impact of this slower dissolution is unknown. The additional treatment will allow the Sponsor to assess the effect of reduced stomach acidity on the PK of LOXO-305 by raising the gastric pH with omeprazole, a PPI.

Additionally, the following clarifications and updates were made:

- Previously, the Schedule of Assessments incorrectly stated that oral body temperature and respiratory rate assessments would be conducted on Day 1, Day 4, Day 8, and Day 11; the Schedule of Assessments has been updated to reflect that oral body temperature and respiratory rate assessments will be conducted at Screening, Day -1, and EOT/Day 25 or ET only.
- Exclusion criterion #8 has been updated to remove the requirement for polymerase chain reaction confirmation to detect presence of an active virus before enrolment for subjects who are positive for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) by antibody. Therefore, any subject who is positive for HBsAg, HCV, or HIV by antibody will be excluded.
- The PK parameter, area under the concentration-time curve from hour 0 to 24 hours (AUC_{0-24}), will be analysed as part of the mixed effects model.
- The inclusion of the PK parameter, apparent first order terminal elimination rate constant (Kel), is redundant as apparent terminal elimination rate constant (λ_Z) will be calculated.
- The statistical comparisons of interest are now:
    - Treatment A compared with Treatment B
    - Treatment A compared with Treatment C.
- In exclusion criterion #16 and concomitant medications and other restrictions, it has been clarified that while concomitant medication of PPIs is prohibited, this is with the exception of omeprazole administered for the purposes of this study and in accordance with the Protocol.

Minor updates:

- The synopsis and study title was updated accordingly to the changes in the protocol body, as applicable.
- The amendment/version number and date were updated throughout the protocol.
- Typographical errors and formatting errors were corrected, and minor clarifications were made, as necessary.