Protocol LOXO-BTK-20010

A Phase I, Open-label, Fixed-sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on CYP1A2, CYP2C9, and CYP2C19 Substrates Using a Probe Drug Cocktail in Healthy Subjects

NCT06215430

Approval date: 10-Dec-2020

Protocol

A Phase I, Open-label, Fixed-sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on CYP1A2, CYP2C9, and CYP2C19 Substrates using a Probe Drug Cocktail in Healthy Subjects

Protocol Status: Final
Protocol Date: 9 December 2020
Protocol Version: 1.0

Investigational Medicinal Product: LOXO-305

Protocol Reference Number: LOXO-BTK-20010
Covance Study Number: 8419689
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

Coordinating Investigator Study Site:
Covance Clinical Research Unit Inc.
1341 West Mockingbird Lane, Suite 200E
Dallas, Texas 75247
USA

Up to 2 additional sites in the United States may be utilized.

Sponsor Signatory:
PPD

Coordinating Investigator:
PPD

SPONSOR APPROVAL

I have read the protocol and approve it:

10-Dec-20 | 07:20:26 PST

Date

INVESTIGATOR AGREEMENT

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

PPD

09 DEC 2020
Date

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 Tel (main): PPD
Sponsor's Study Contact	PPD Director, Clinical Operations Loxo Oncology, Inc. Tel (mobile): PPD Tel (alternative contact): PPD Email: PPD
Sponsor's Medical Contact	PPD Consulting to Loxo Oncology, Inc. Tel (mobile): PPD Email: PPD
Serious Adverse Event Reporting	Email: SAEIntake@covance.com
Study Site(s)	**Coordinating Investigator Study Site** Covance Clinical Research Unit Inc. 1341 West Mockingbird Lane, Suite 200E Dallas, Texas 75247 USA Up to 2 additional sites in the United States may be utilized.
Coordinating Investigator	PPD Covance Clinical Research Unit Inc. 1341 West Mockingbird Lane, Suite 200E Dallas, Texas 75247 USA Tel: PPD Tel (cell): PPD
Sub-investigator(s)	Obtain information from Form FDA 1572s
Clinical Laboratory(s)	Covance Clinical Research Unit Inc. 1341 West Mockingbird Lane, Suite 200E Dallas, Texas 75247 USA Each additional site will use their local laboratory for safety analyses.

Bioanalytical Laboratory	Alturas Analytics, Inc. 1324 Alturas Drive Moscow, Idaho 83843 USA Tel (main): (208) 883-3400 Email: jzimmer@alturasanalytics.com
Statistician	PPD Covance Tel: PPD Email: PPD
Protocol Medical Writer	PPD Covance Tel: PPD Email: PPD

SYNOPSIS

Study Title

A Phase I, Open-label, Fixed-sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on CYP1A2, CYP2C9, and CYP2C19 Substrates using a Probe Drug Cocktail in Healthy Subjects

Objectives

The primary objective of the study is to assess the effect of multiple oral doses of LOXO-305 on the pharmacokinetic (PK) of single oral doses of caffeine (cytochrome P450 [CYP]1A2 substrate), S-warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) in healthy subjects.

The secondary objective of the study is to assess the safety and tolerability of multiple oral doses of LOXO-305 when administered alone, and coadministered with a single oral dose of probe drug cocktail.

Study Design

This is a Phase 1, open-label, 2-period, fixed-sequence drug-drug interaction study to investigate the effect of multiple oral doses of LOXO-305 on the PK of single oral doses of caffeine (CYP1A2 substrate) and its metabolite paraxanthine, S-warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) in healthy subjects.

In Period 1, Day 1, 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg vitamin K (tablets), will be administered in the morning following a fast of at least 10 hours predose and 2 hours postdose. Blood samples for concentrations of the substrates (caffeine/paraxanthine, omeprazole, and S-warfarin) in plasma will be collected CCI . Of the samples collected for concentrations of each substrate in plasma CCI postdose on Day 1, samples will be analyzed for concentration of caffeine/paraxanthine from CCI postdose, for concentration of omeprazole from CCI postdose, and S-warfarin from CCI .

There will be a washout period of 5 days between administration of the probe drug cocktail on Day 1 and the first dose of LOXO-305 on Day 6.

In Period 2, on Days 6 through 19, oral doses of 200 mg LOXO-305 will be administered once daily (QD) for 14 consecutive days in the morning at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour). On Day 15, LOXO-305 will be coadministered with 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg of vitamin K (tablets), at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour) following a fast of at least 10 hours predose and 2 hours postdose. On Days 7 through 11, and Days 13, 14, 16, 18, and 19, subjects will fast for at least 2 hours predose and 1 hour postdose. On Days 6, 12, and 17 where clinical laboratory evaluations are performed, subjects will fast for at least 8 hours predose and 1 hour postdose. Blood samples for concentrations of LOXO-305 in plasma will

be collected and analyzed CCI [redacted]. Samples collected CCI [redacted] will be collected prior to LOXO-305 dosing on Days 16 through 19. Blood samples for concentrations of the substrates (caffeine/paraxanthine, omeprazole, and S-warfarin) in plasma will be CCI [redacted]. Of the samples collected for concentrations of each substrate in plasma CCI [redacted] samples will be analyzed for concentration of caffeine/paraxanthine from CCI [redacted], for concentration of omeprazole from CCI [redacted], and for concentration of S-warfarin from CCI [redacted].

To assess their eligibility to enter the study, potential subjects will be screened within 34 days (Days -35 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in).

Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 23 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Dosing of probe drug cocktail will occur on Day 1 and Day 15 and dosing of LOXO-305 will occur on Days 6 through 19. 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 to receive a dose of study drug; this definition excludes screen failure subjects. Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

In this study, physical examinations, 12-lead electrocardiograms (ECGs), vital sign measurements, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, hematology panel, 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 (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 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

Up to 16 healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. Every attempt will be made to enroll at least 4 subjects of each sex in the study.

Main Criteria for Inclusion

Male subjects, and female subjects of non-childbearing potential must meet the following criteria:

- Between 18 and 55 years of age, inclusive, at Screening
- Within body mass index (BMI) range 18.0 to 32.0 kg/m^2, inclusive, at Screening
- In good general health, based on medical history, physical examination findings, vital signs, 12-lead ECG, or clinical laboratory evaluations at Screening and/or Check-in (Day -1), as determined by the Investigator (or designee)

Investigational Medicinal Products, Dose, and Mode of Administration

Subjects will receive each of the following treatments throughout the study:

- In Period 1, Day 1, 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) will be administered as a single dose of probe drug cocktail, along with 10 mg vitamin K (2 × 5 mg tablets), in the morning following a fast of at least 10 hours predose and 2 hours postdose. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose administration.
- In Period 2, on Days 6 through 19, oral doses of 200 mg (2 × 100 mg tablets) LOXO-305 will be administered QD for 14 consecutive days in the morning at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour). On Day 15, LOXO-305 will be coadministered with 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg vitamin K (2 × 5 mg tablets), at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour) following a fast of at least 10 hours predose and 2 hours postdose. On Days 7 through 11, and Days 13, 14, 16, 18, and 19, subjects will fast for at least 2 hours predose and 1 hour postdose. On Days 6, 12, and 17 where clinical laboratory evaluations are performed, subjects will fast for at least 8 hours predose and 1 hour postdose. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose 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.

Duration of Subject Participation in the Study:

Planned Enrollment/Screening Duration: Approximately 34 days (Days -35 to -2).

Length of CRU Confinement: Up to 24 days (Days -1 to 23).

Planned Study Conduct Duration: Up to 67 days (Screening through follow-up call).

Criteria for Evaluation:

Pharmacokinetics:

Serial blood samples for plasma concentration analysis of caffeine/paraxanthine, omeprazole, and S-warfarin will be collected from predose through CCI . Serial blood samples for plasma concentration analysis of LOXO-305 will be collected CCI . Samples collected CCI will be collected prior to LOXO-305 dosing on Days 16 through 19.

The following PK parameters will be calculated, whenever possible, based on the plasma concentrations of caffeine/paraxanthine, omeprazole, S-warfarin, and LOXO-305 (as appropriate): area under the concentration-time curve (AUC) from hour 0 to 24 hours postdose (AUC_{0-24}), AUC from hour 0 to the last measurable concentration (AUC_{0-t}), AUC from hour 0 extrapolated to infinity (AUC_{0-inf}), percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$), apparent systemic clearance (CL/F), apparent plasma terminal elimination half-life ($t_{½}$), maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), apparent terminal elimination rate constant (λ_z), mean residence time (MRT), apparent volume of distribution at the terminal phase (V_z/F), and AUC_{0-24} and AUC_{0-48} ratio of paraxanthine to caffeine (MRAUC; caffeine/paraxanthine only).

Safety:

Safety will be monitored with HDYF? inquiries, clinical laboratory evaluations, vital sign measurements, 12-lead ECGs, and physical examinations.

Statistical Methods

Pharmacokinetics:

The primary analysis planned for this study is a mixed effect model that includes treatment as a fixed effect and subject as a random effect. The analysis will be performed on the natural log (ln)-transformed PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) and 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 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 will be probe drugs alone (caffeine and its metabolite paraxanthine, omeprazole, and S-warfarin) versus probe drugs (caffeine and its metabolite paraxanthine, omeprazole, and S-warfarin) coadministered with LOXO-305. The ratio of paraxanthine to caffeine will be summarized.

Safety:

All safety assessments, including AEs, SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and 12-lead ECGs, will be tabulated, and summarized where possible, using descriptive methodology by treatment and,

as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of study drug on Day 1, Period 1. No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

The specific procedures will be documented in the Statistical Analysis Plan.

TABLE OF CONTENTS

TITLE PAGE 1
SPONSOR APPROVAL 2
INVESTIGATOR AGREEMENT 3
STUDY IDENTIFICATION 4
SYNOPSIS 6
TABLE OF CONTENTS 11
LIST OF TABLES AND FIGURES 13
LIST OF ABBREVIATIONS 14
1. INTRODUCTION 17
1.1. Background 17
1.2. Nonclinical Pharmacokinetics and Toxicology Summary 17
1.3. Potential for Drug-drug Interactions 19
1.4. Summary of Clinical Experience 20
1.4.1. Safety 21
1.4.2. Pharmacokinetics 22
1.5. Study Rationale 25
1.6. Risk Assessment 26
2. OBJECTIVES AND ENDPOINTS 27
2.1. Objectives 27
2.1.1. Primary Objective 27
2.1.2. Secondary Objective 27
2.2. Endpoints 27
2.2.1. Primary Endpoints 27
2.2.2. Secondary Endpoints 27
3. INVESTIGATIONAL PLAN 28
3.1. Overall Study Design and Plan 28
3.2. Discussion of Study Design 30
3.3. Selection of Doses in the Study 30
3.3.1. LOXO-305 30
3.3.2. Probe Drug Cocktail 30
4. SELECTION OF STUDY POPULATION 32
4.1. Screening Procedures 32
4.2. Check-in Procedures (Day -1) 32
4.3. Inclusion Criteria 33
4.4. Exclusion Criteria 35
4.5. Subject Number and Identification 39
4.6. Removal of Subjects from Study Participation 39
5. STUDY TREATMENTS 41
5.1. Description, Storage, Packaging, and Labeling 41

5.2. Study Treatment Administration 41
5.3. Randomization 42
5.4. Blinding 42
5.5. Treatment Compliance 42
5.6. Drug Accountability 43
6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS 44
6.1. Concomitant Therapies 44
6.2. Diet, Fluid, and Activity Control 44
7. STUDY ASSESSMENTS AND PROCEDURES 46
7.1. Pharmacokinetic Assessments 46
7.1.1. Pharmacokinetic Blood Sample Collection and Processing 46
7.1.2. Analytical Methodology 46
7.2. Genotyping 46
7.3. Safety and Tolerability Assessments 46
7.3.1. Adverse Events 47
7.3.2. Clinical Laboratory Evaluations 48
7.3.3. Vital Signs 48
7.3.4. 12-lead Electrocardiogram 48
7.3.5. Physical Examination 49
8. SAMPLE SIZE AND DATA ANALYSIS 50
8.1. Determination of Sample Size 50
8.2. Analysis Populations 50
8.3. Pharmacokinetic Analysis 50
8.3.1. Descriptive Analysis 51
8.3.2. Statistical Methodology 51
8.4. Safety Analysis 52
8.5. Data Handling and Record Keeping 52
8.6. Quality Control and Quality Assurance 53
9. ADMINISTRATIVE ASPECTS 54
9.1. Change in Protocol 54
9.2. Site Initiation Visit/Investigator Meeting 54
9.3. Disclosure 54
9.4. Monitoring 54
9.5. Institutional Review Board 54
9.6. Informed Consent 55
9.7. Records 55
9.8. Reference to Declaration of Helsinki/Basic Principles 55
9.9. Financing and Insurance 56
10. REFERENCES 57
11. APPENDICES 58

Appendix 1: Adverse Event Reporting 59
Appendix 2: Clinical Laboratory Evaluations.....63
Appendix 3: Total Blood Volume.....64
Appendix 4: Schedule of Assessments 65

LIST OF TABLES AND FIGURES

Table 1: Pharmacokinetic Parameters of LOXO-305 in Cancer Patients (Study LOXO-BTK-18001) at Steady State (Cycle 1 Day 8) 23
Table 2: Study Drugs 41

Figure 2: Dose-Exposure Correlation Assessed by AUC_{0-8} vs Dose for Cycle 1 Day 8 ...25
Figure 3: Study Schematic 29

LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve from hour 0 extrapolated to infinity
ADL	Activities of Daily Living
AE	adverse event
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 from hour 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BP	blood pressure
BSEP	bile salt exporter pump
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CI	confidence interval(s)
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent systemic clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
COVID-19	SARS-CoV-2
CRF	Case Report Form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDYF?	How Do You Feel?
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
IC_{90}	concentration required for 90% inhibition
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IgM	immunoglobulin M
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LFT	liver function test(s)
Ln	natural log
LS	least squares
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
MRT	mean residence time
NHL	non-Hodgkin lymphoma
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OCT	organic cation transporter
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell(s)
RP2D	recommended Phase 2 dose
SAD	single ascending dose
SAE	serious adverse event(s)
SAP	Statistical Analysis Plan
SD	standard deviation

SDD	spray-dried dispersion
SLL	small lymphocytic lymphoma
SOC	system organ class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent plasma terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time to maximum observed plasma concentration
TSH	thyroid-stimulating hormone
UA	urinalysis
V_z	volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell(s)
WHO	World Health Organization
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, LOXO-305.[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. LOXO-305 is distinct from the approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) in several important ways including on the basis of its selectivity, favorable absorption, distribution, metabolism, and excretion properties, and non-covalent binding mode.[2] These features enable LOXO-305 to achieve pharmacokinetic (PK) exposures that exceed the BTK concentration resulting in 90% inhibition (IC_{90}) at trough, and thus deliver tonic BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. Moreover, the non-covalent binding mode of LOXO-305 is unaffected by BTK C481 substitutions, a common mechanism of drug resistance described for all available covalent inhibitors.[3,4,5,6,7] Finally, LOXO-305 is also a highly selective molecule that is more than 300-fold more selective for BTK versus 370 other kinases tested with no significant inhibition of non-kinase off-targets at 1 μM, thus limiting the potential for off-target mediated toxicities. Collectively, these unique properties of LOXO-305 are expected to deliver more potent, continuous, and selective inhibition of BTK in a variety of settings, potentially resulting in increased efficacy. Of note, the activity of LOXO-305 in diverse preclinical model systems supports this underlying hypothesis.[2]

LOXO-305 is a small molecule that was designed to block the adenosine triphosphate (ATP) binding site of the BTK kinase competitively. There is no evidence of irreversible binding. LOXO-305 has a molecular weight of approximately 500 g/mol. LOXO-305 will be supplied as an immediate-release tablet containing 25 mg or 100 mg of drug substance.

1.2. Nonclinical Pharmacokinetics and Toxicology Summary

LOXO-305 had high permeability in vitro, but low aqueous solubility. To reduce the variability in oral absorption, a spray-dried dispersion (SDD) tablet formulation was developed that showed consistent oral bioavailability of approximately 50% in rats and 80% in dogs. The bioavailability of the SDD formulation was also not dependent on feeding state in dogs.

As is common in rodents, oral exposure of LOXO-305 was consistently much higher in female rats than in males given the same dose of LOXO-305. The sex difference was also apparent after intravenous (IV) administration of LOXO-305. There was no difference in the PK of LOXO-305 between sexes of dog, and none is expected in other non-rodent species, including humans.

The volume of distribution (V_z) of LOXO-305 ranged from approximately 2 L/kg in the dog to 5 L/kg in the male rat, which indicates that LOXO-305 distributes into tissues. LOXO-305 had protein binding of approximately 95% in human plasma. A somewhat lower extent of binding (approximately 82% to 92%) was observed across mouse, rat, rabbit, and dog.

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 clone expressed cytochrome P450 (CYP) enzymes and human liver microsomes indicate that CYP3A4 is the primary CYP enzyme that metabolizes LOXO-305. It is also a substrate for direct glucuronidation.

In long-term hepatocyte incubations, LOXO-305 was metabolized by both oxidation and glucuronidation. Inhibition of oxidative metabolism by addition of the P450 inhibitor 1-aminobenzotriazole showed that oxidative metabolism is CYP dependent. All metabolites formed by human hepatocytes were also formed in rat and/or dog hepatocytes supporting the use of rat and dog for nonclinical safety assessment.

Renal clearance of LOXO-305 in male and female rats was negligible. No data on renal clearance are available in other species; however, the renal excretion pathway is often conserved across species, and therefore no renal clearance would be expected in humans.

In a Good Laboratory Practice (GLP) in vitro assay for human ether-à-go-go-related gene (hERG) activity, the concentration resulting in 50% inhibitory concentration (IC_{50}) for the inhibitory effects of LOXO-305 on hERG potassium currents was CCI µM, which is approximately CCI-fold higher than the maximum unbound concentration of LOXO-305 in patients treated with the dose of 200 mg once daily (QD). There were no LOXO-305-related changes in any cardiovascular endpoints including QTc at single doses up to 60 mg/kg in the GLP cardiovascular study in the conscious telemetry-instrumented dog. The maximum observed plasma concentration (C_{max}) for this dose was 10000 ng/mL, which is approximately CCI above the predicted C_{max} (CCI ng/mL) at the proposed clinical therapeutic dose of 200 mg QD. Furthermore, there were no LOXO-305-related abnormalities in rhythm or waveform morphology in the GLP 28-day repeated-dose toxicity study in dogs at the low and mid-dose groups based on comparison of predose and postdose electrocardiogram (ECG) recordings. The high dose (90/60 mg/kg/dose twice daily [BID]) was not evaluated as animals in this group were moribund/debilitated and were terminated on Day 13. Mean QTc interval was statistically significantly prolonged (+6%; +15 msec) on Day 26 of the dosing phase in males administered 30/10 mg/kg/dose BID compared with controls. The prolongation in QTc for males was below the 10% increase or the threshold reported for canines exposed to therapeutic concentrations of drugs known to cause QT prolongation in humans.[8] Therefore, the QTc changes were considered physiologically unimportant, and thus not deemed to be adverse. Together, these data indicate that LOXO-305 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias in patients.

There were no LOXO-305-related findings on the central nervous system when evaluated in rat functional observational battery tests and locomotor activity assessments after 4 weeks of dosing or during recovery at doses of up to 500 mg/kg/dose BID in male rats and 175 mg/kg/dose BID in female rats as part of the GLP 28-day repeat-dose study.

LOXO-305 had no effect on respiration rate in the dog at doses up to 10 mg/kg/dose BID.

Targets of toxicity were characterized in repeated-dose studies conducted in 2 relevant toxicity species. Certain targets (the hematopoietic and lymphoid systems) were found in both the rat and the dog. Rat-specific changes in the pancreas are species-specific and seen

with other BTK inhibitors. Dog-specific changes in lung and large intestine were lesions contributing to moribundity in high-dose animals in the 28-day study. Doses evaluated in the 28-day dog study demonstrated a steep dose-response curve for toxicity and pronounced changes in hematologic parameters at high exposures. Additionally, in dogs treated for 3 months, 2 male dogs at 5 mg/kg BID (the highest dose tested) were observed to have eye lesions via both ophthalmic and microscopic examination. Findings were observed in both eyes of these animals and consisted of very slight to slight multifocal or focal areas of corneal opacity in the center of the cornea along with constellation histopathological findings suggestive of minimal to mild corneal injury. The time of onset of these effects is unknown, as ophthalmic exams were only performed prior to the start of dosing and during the last week of the study; however, no eye effects were observed in the previous 28-day study. No ocular findings were observed in females. See the IB for additional details.[1]

LOXO-305 was not mutagenic in 2 bacterial reverse mutation assays and was negative in a non-GLP micronucleus assay using Chinese hamster ovary cells. LOXO-305 was positive for the induction of micronuclei via an aneugenic mechanism in the absence and presence of the exogenous metabolic activation system in a GLP in vitro micronucleus assay in human peripheral blood lymphocytes. However, LOXO-305 was negative in a GLP in vivo micronucleus assay in rats at doses up to and including a dose of CCI mg/kg. The C_{max} at the no observed effect level of CCI mg/kg was CCI ng/mL for males and CCI ng/mL for females.

LOXO-305 was not found to be phototoxic when evaluated in an in vitro neutral red uptake phototoxicity assay.

1.3. Potential for Drug-drug Interactions

LOXO-305 showed no detectable inhibition (IC_{50} > CCI µM) of CYP1A2, CYP2B6, CYP2C19, and CYP2D6, and weak inhibition of CYP2C8, CYP2C9, and CYP3A4 in human liver microsomes. After pre-incubation of microsomes with LOXO-305 and nicotinamide adenine dinucleotide phosphate prior to addition of CYP450 probe substrate, the CYP3A4 inhibitory potency of LOXO-305 was increased, suggesting the potential for time-dependent inhibition of CYP3A4. Further kinetic evaluation confirmed that LOXO-305 is a time-dependent inhibitor of CYP3A4.

In an in vitro hepatocyte assay, LOXO-305 induced messenger RNA (mRNA) for CYP3A4, CYP3A5, CYP2B6, and CYP2C19. For both CYP2B6 and CYP2C19, an increase in activity was seen. For CYP3A4, LOXO-305 did not cause an increase in activity, likely due to concurrent inhibition of CYP3A4 by LOXO-305. LOXO-305 caused a decrease in mRNA for CYP1A2 but did not lead to a reduction of CYP1A2 activity. In the study, CYP2D6, CYP2C8, and CYP2C9 mRNA were not induced.

In vitro LOXO-305 inhibited P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein (MATE) 1, and MATE2K. LOXO-305 did not inhibit organic anion transporter (OAT) 1 and weakly inhibited organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, OAT3, and bile salt exporter pump (BSEP).

LOXO-305 is a substrate of P-gp and BCRP. It is not a substrate of the hepatic transporters OCT1, OATP1B1, OATP1B3, or BSEP.

1.4. Summary of Clinical Experience

LOXO-305 is currently being studied in an ongoing global Phase 1/2 first-in-human study, LOXO-BTK-18001 (the BRUIN Study), in patients with previously treated chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) or non-Hodgkin lymphoma (NHL). The starting dose of LOXO-305 was 25 mg QD.

As of September 27, 2020, safety data were available from a total of 330 patients treated in the LOXO-BTK-18001 study. This includes 324 patients treated at doses ranging from 25 mg QD to 300 mg QD in Phase 1/2 Monotherapy cohorts, and 6 patients treated in Phase 1b Combination Arm A (LOXO-305 200 mg QD plus venetoclax 400 mg QD [after ramp-up] Section 1.4.1).

As of September 30, 2020, PK data were available from 181 patients enrolled in the LOXO-BTK-18001 study (Section 1.4.2).

As of November 23, 2020, LOXO-305 had been recently investigated in 1 study in healthy volunteers (LOXO-BTK-20014), which was completed. LOXO-BTK-20014 was a pilot food-effect crossover study evaluating the effects of food and a proton pump inhibitor (omeprazole) on the PK of LOXO-305 where 10 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days, each followed by a washout period.

As of November 23, 2020, four additional studies were ongoing in healthy volunteers (LOXO-BTK-20006, LOXO-BTK-20017, LOXO-BTK-20007, and LOXO-BTK-20008).

LOXO-BTK-20006 is a drug-drug interaction (DDI) study evaluating the effects of a strong CYP3A4 inhibitor (itraconazole) and a strong CYP3A4 inducer (rifampin) on the PK of LOXO-305 where, at the time of this protocol's development, 3 healthy volunteers were given 1 dose of 200 mg of LOXO-305, 12 healthy volunteers were given 200 mg of LOXO-305 on 2 separate days (1 of which was co-administered with itraconazole), each followed by a washout period, and 12 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days (2 of which were co-administered with rifampin), each followed by a washout period.

LOXO-BTK-20017 is a single ascending dose (SAD) study evaluating the safety and tolerability of LOXO-305 at 300 mg, 600 mg, 800 mg, and 900 mg doses, where, at the time of this protocol's development, 6 healthy volunteers were given a single dose of 300 mg LOXO-305, 6 healthy volunteers were given a single dose of 600 mg LOXO-305, 6 healthy volunteers were given a single dose of 800 mg LOXO-305, and 6 healthy volunteers were given a single dose of 900 mg LOXO-305.

LOXO-BTK-20007 is a 2-part study of the absorption, metabolism, excretion, and the absolute bioavailability of [^{14}C]-LOXO-305 where, at the time of this protocol's development, 4 subjects were given a single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) as an oral solution and 5 subjects were given a single oral dose of 200 mg LOXO-305 as 2 × 100-mg tablets followed 2 hours later by a single dose of < 100 µg of [^{14}C]-LOXO-305 (containing ~1 µCi of radioactivity [microtracer]) administered as an IV push over approximately 2 minutes.

LOXO-BTK-20008 is a DDI study evaluating the effects of LOXO-305 on the PK of a sensitive CYP3A4 substrate (midazolam) where, at the time of this protocol's development, 15 healthy volunteers were given 200 mg QD of LOXO-305 on 13 consecutive days (1 day of which was co-administered with IV midazolam and 1 day of which was co-administered with oral midazolam).

1.4.1. Safety

As of September 27, 2020, 330 patients were treated in the LOXO-BTK-18001 study and received LOXO-305. This includes 324 patients treated at doses ranging from 25 mg QD to 300 mg QD in Phase 1/2 Monotherapy cohorts, and 6 patients treated in Phase 1b Combination Arm A (LOXO-305 200 mg QD plus venetoclax 400 mg QD [after venetoclax ramp-up]). A full summary of treatment-emergent adverse events (TEAEs) for patients in the study is provided in the LOXO-305 IB and the Investigator is directed to the safety information described in that document.[1] A summary of safety for LOXO-305 given as monotherapy to patients in the LOXO-BTK-18001 study is provided below.

- In the 324 patients in the Phase 1/2 Monotherapy cohorts, TEAEs reported in ≥ 10% of patients (n = 33 or more) were fatigue (20.1% total, 8.3% related), diarrhea (17.0% total, 8.6% related), and contusion (13.0% total, 9.0% related). Drug-related TEAEs were reported in 156 of 324 patients (48.1%) in the Phase 1/2 Monotherapy cohorts. The most frequently reported drug-related TEAEs for LOXO-305 (those in > 5% of patients overall) were contusion (9.0%), diarrhea (8.6%), and fatigue (8.3%). All other drug-related TEAEs were reported in < 5% of patients (ie, < 17 patients each). Treatment-emergent AEs of severity Grade 3 or 4 were reported in 87 of 324 patients (26.9%) in the Phase 1/2 Monotherapy cohorts, with 41 (12.7%) of these Grade 3 or 4 AEs reported as related to study drug.

- On-study death (death within 28 days of the last dose of study drug) due to a Grade 5 (fatal) AE was reported in 4 of 324 patients (1.2%) in the Phase 1/2 Monotherapy cohorts. One Grade 5 AE, *Enterococcus faecium*-related septic shock, was considered to be related to study drug (further details are provided in the LOXO-305 IB[1]). All other Grade 5 AEs were considered to be not related to study drug; these included pneumonia fungal, shock, and pleural effusion.

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20014 study (headache, nausea, and vomiting), were all Grade 1 in severity and considered to be related to LOXO-305. All 3 events were reported by 1 subject and resolved within 1 to 1.5 days.

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20006 study (intermittent belching, bloating, insect bite, aphthous ulcer, nausea, intermittent diarrhea [x2], muscle twitch), were all Grade 1 in severity, and bloating, 1 instance of intermittent diarrhea, and intermittent belching were considered to be related to LOXO-305 and rifampin. All 7 AEs were reported by 3 subjects and all events resolved prior to End of Treatment (EOT; preliminary data on file at the time of this protocol's development).

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20017 study (headache [observed at the 300 mg LOXO-305 dose], and headache [x2], intermittent headache, and petechial rash left thigh [observed at the 900 mg LOXO-305 dose]), were all Grade 1 in severity. One instance of headache observed at the 300 mg LOXO-305 dose and 1 instance observed at the 900 mg LOXO-305 dose, the intermittent headache, and the petechial rash left thigh were considered to be related to LOXO-305. All five AEs were reported by 4 subjects and resolved within 2 hours to 5 days of onset (preliminary data on file at the time of this protocol's development).

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in Part 1 of the LOXO-BTK-20007 study (bloody nose, headache, loose stool [x2], red bumps on left knee, small abrasion to right elbow), were all Grade 1 in severity and headache was considered to be related to LOXO-305. All 7 AEs were reported by 4 subjects and all events resolved within 1 to 2 days (preliminary data on file at the time of this protocol's development).

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in Part 2 of the LOXO-BTK-20007 study (tenderness at left venipuncture site [x2], bruising to left antecubital secondary to phlebotomy [x2], bruising to right antecubital secondary to phlebotomy, and allergic reaction), were all Grade 1 in severity and no events were considered to be related to LOXO-305. All 6 AEs were reported by 4 subjects and all events resolved within 1 to 2 days (preliminary data on file at the time of this protocol's development).

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20008 study (injection site pain, nasal congestion, flatulence, constipation, increased urinary frequency, facial rash, and skin tear from tape at IV site), were all Grade 1 in severity, and flatulence, constipation, and increased urinary frequency were considered to be related to LOXO-305. All 7 AEs were reported by 3 subjects and all events resolved within 1 to 8 days (preliminary data on file at the time of this protocol's development).

As part of each clinical trial conducted in patients or healthy volunteers, ECG and vital signs are performed at intervals specified by protocol. For study LOXO-BTK-18001 conducted in patients, no clinically significant findings of QTc prolongation have been identified in 330 patients as of September 27, 2020 (LOXO-305 IB[1]). In addition, there have been no clinically significant abnormal findings in vital signs and ECG data in the studies investigating LOXO-305 conducted in healthy volunteers as of November 23, 2020 (preliminary data on file at the time of this protocol's development).

1.4.2. Pharmacokinetics

As of September 30, 2020, PK data were available from 181 patients enrolled in the LOXO-BTK-18001 study. Steady-state PK parameters of LOXO-305 in these cancer patients could be derived from data collected on Cycle 1 Day 8 (Figure 1), and are shown in Table 1. These data show that LOXO-305 is absorbed after oral administration with a median time to maximum observed plasma concentration (t_{max}) of approximately 2 hours and low clearance (Table 1). Due to the limited sampling interval (0-8 hours), imputation for the 24-hour sample was made from Cycle 1 Day 8 predose sample, leading to an estimated plasma half-life of

approximately 20 hours. Maximum observed plasma concentration and area under the plasma concentration-time curve (AUC) of LOXO-305 showed increase proportional to dose (Figure 2). Following administration of the recommended Phase 2 dose (RP2D) 200 mg QD, mean trough plasma levels of LOXO-305 exceeded the concentration required for 96% inhibition of BTK in vitro (IC_{50} = CCI ng/mL, IC_{96} = CCI ng/mL). Further details may be found in the IB.[1]

Pharmacokinetic data following oral administration of a 200-mg dose of LOXO-305 in tablet form in healthy volunteers in the LOXO-BTK-20014 study indicate that there was little effect of either a standard meal or the proton pump inhibitor omeprazole on the PK of LOXO-305.

Table 1: Pharmacokinetic Parameters of LOXO-305 in Cancer Patients (Study LOXO-BTK-18001) at Steady State (Cycle 1 Day 8)

Dose Level	N	C_{max} (ng/mL) Geo mean (%CV)	t_{max} (h) Median (min, max)	AUC_{0-8} (ng*h/ mL) Geo mean (%CV)	AUC_{0-24} (ng*h/mL) Geo mean (%CV)	CL/F (L/h) Geo mean (%CV)	$t_{1/2}$ (h) Geo mean (%CV)	Ratio AUC_{0-8} Day 8/Day 1 Geo mean (%CV)
25 mg QD	5	734 (11.0%)	2 (1, 8)	4240 (12.4%)	9800 (25.8%)	1.55[a] (69.6%)	18.2[a] (60.1%)	1.44 (23.0%)
50 mg QD	6	1420 (19.2%)	1.5 (1, 4)	8660 (24.7%)	20100 (34.9%)	2.62[b] (36.7%)	17.6[b] (39.6%)	1.51 (25.9%)
100 mg QD	9	3910 (35.6%)	2 (1, 4)	22000 (37.2%)	52400 (39.7%)	0.968[c] (63.0%)	22.2[c] (33.9%)	1.88 (42.8%)
150 mg QD	20	4680 (29.1%)	2 (1, 8)	28000 (29.6%)	64400 (39.6%)	1.36[d] (66.7%)	18.1[d] (51.8%)	1.74 (24.9%)
200 mg QD	99	5770 (47.7%)	2 (1, 8)	36900 (40.8%)	91000 (42.0%)	1.14[e] (61.8%)	19.9[e] (56.2%)	1.69[h] (29.6%)
250 mg QD	25	8100 (28.1%)	2 (1, 4)	49700 (31.3%)	111000 (38.7%)	1.26[f] (1.08%)	17.4[f] (50.6%)	1.68 (24.5%)
300 mg QD	17	10700 (26.6%)	2 (1, 4)	65800 (35.9%)	158000 (49.2%)	1.63[g] (42.5%)	30.1[g] (102%)	2.15 (31.2%)

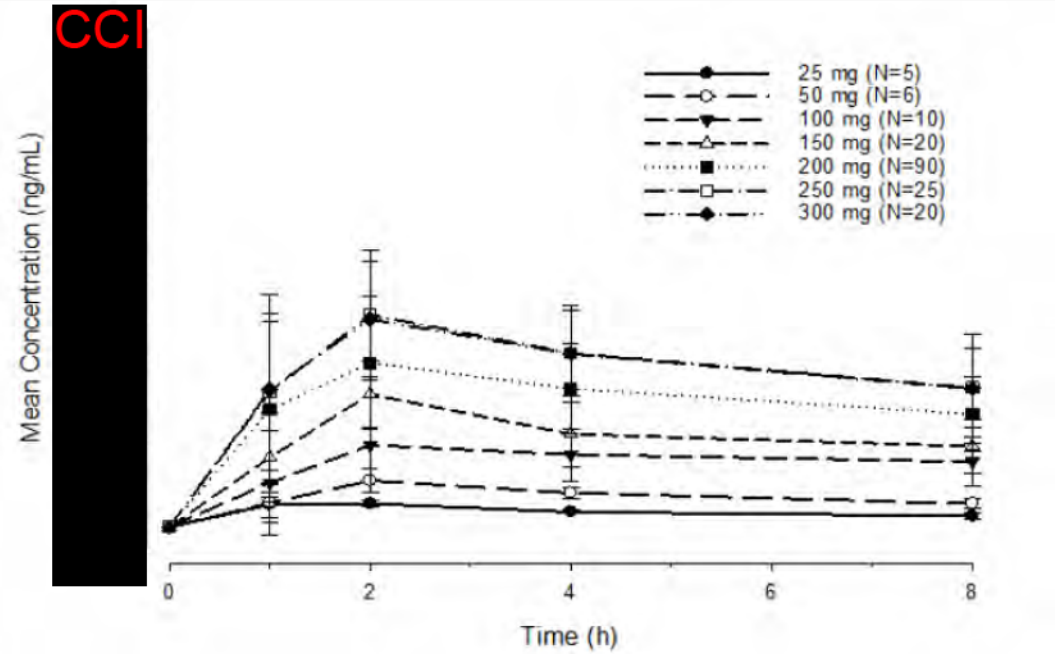
Abbreviations: AUC_{0-8} = area under the concentration-time curve from time 0 to 8 hours; AUC_{0-24} = area under the concentration-time curve from time 0 to 24 hours; CL/F = apparent oral clearance; C_{max} = maximum drug concentration; Geo mean = Geometrical mean; N = number of subjects; QD = once daily; CV = coefficient of variation; $t_{1/2}$ = half-life; t_{max} = time of maximal plasma concentration.

[a] N= 4, [b] N= 5, [c] N= 8, [d] N= 18, [e] N= 64, [f] N= 21, [g] N= 16, [h] N= 73

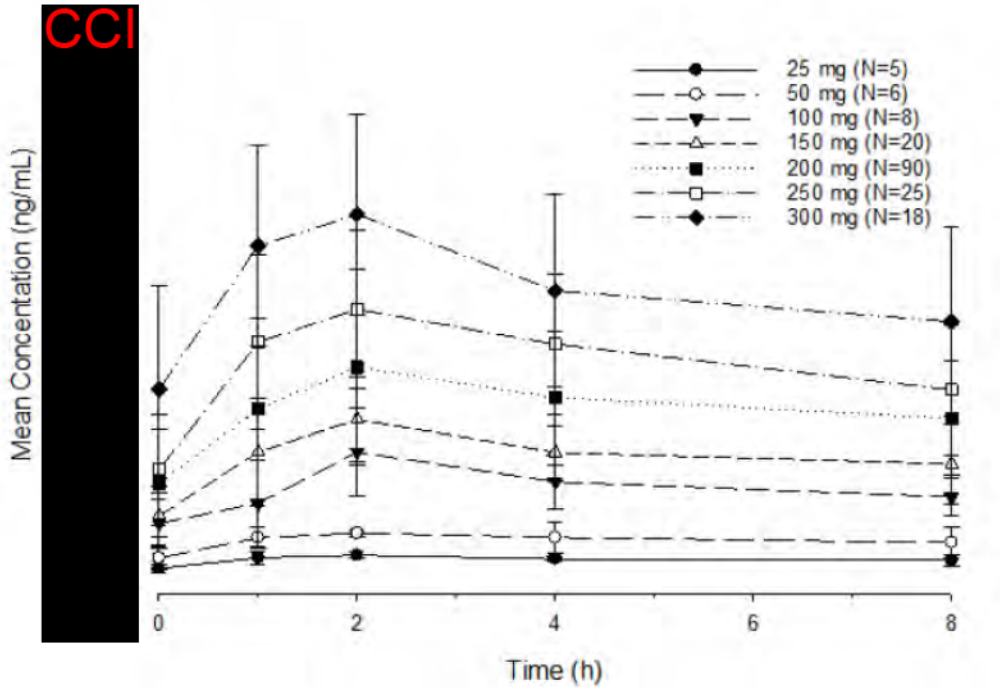
SDTM Transfer: September 30, 2020

CCI

CCI


Mean Concentration (ng/mL)
25 mg (N=5)
50 mg (N=6)
100 mg (N=10)
150 mg (N=20)
200 mg (N=90)
250 mg (N=25)
300 mg (N=20)
0
2
4
6
8
Time (h)

CCI


Mean Concentation (ng/mL)
25 mg (N=5)
50 mg (N=6)
100 mg (N=8)
150 mg (N=20)
200 mg (N=90)
250 mg (N=25)
300 mg (N=18)
0
2
4
6
8
Time (h)

SDTM Transfer: September 30, 2020

Preliminary and interim plasma concentration data from ongoing study LOXO-BTK-20008 indicate that the dose of 200 mg QD in healthy volunteers produces a LOXO-305 steady-state geometric mean C_{max} of CCI ng/mL and AUC from hour 0 to 24 hours postdose (AUC_{0-24}) of approximately CCI ng*h/mL. These results indicate that the dose of 200 mg QD in this study will provide exposure in the range of the RP2D of LOXO-305 seen in patients, while remaining well under the no observed adverse effect level C_{max} for genotoxicity of approximately CCI ng/mL.

1.5. Study Rationale

The objective of DDI studies is to determine whether potential interactions between an investigational drug and other drugs exist. Drug-drug interaction studies have an important role in drug development,[9] and this study is being performed as part of the development program for LOXO-305.

LOXO-305 showed no detectable inhibition (IC_{50} CCI µM) of CYP1A2, CYP2B6, CYP2C19, and CYP2D6, and weak inhibition of CYP2C8, CYP2C9, and CYP3A4 with inhibitory constant (K_i) values ranging from CCI µM in human liver microsomes. After pre-incubation of microsomes with LOXO-305 and nicotinamide adenine dinucleotide phosphate for 30 minutes prior to addition of CYP450 probe substrate, the CYP3A4 inhibitory potency of LOXO-305 was increased, suggesting the potential for time-dependent inhibition of CYP3A4. Further kinetic evaluation confirmed that LOXO-305 is a time-dependent inhibitor of CYP3A4 with a K_i value of CCI µM and a k_{inact} (maximal inactivation rate constant) value of CCI .15 h^{-1} resulting in a Cl_{inact} value (inactivation clearance) of 8.64 min^{-1} mM^{-1}.

In an in vitro hepatocyte assay, LOXO-305 induced mRNA for CYP3A4, CYP3A5, CYP2B6, and CYP2C19. For both CYP2B6 and CYP2C19, an increase in activity was seen. For CYP3A4, LOXO-305 did not cause an increase in activity, likely due to concurrent inhibition of CYP3A4 by LOXO-305. LOXO-305 caused a decrease in mRNA for CYP1A2 but did not lead to a reduction of CYP1A2 activity. In the study, CYP2D6, CYP2C8, and CYP2C9 mRNA were not induced.

LOXO-305 may have the potential to raise plasma concentrations of drugs that are substrates of CYP2C8, CYP2C9, and CYP3A4 or lower plasma concentrations that are metabolized by CYP1A2, CYP2B6, CYP2C19, or CYP3A4. This study is designed to determine the effect of LOXO-305 on the PK of caffeine (CYP1A2 substrate), S-warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). The effects of LOXO-305 on the PK of other CYP450 substrates will be explored in separate clinical studies. Caffeine, warfarin, and omeprazole are commonly used as index substrates for CYP450 enzymes in DDI studies.[9]

1.6. 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 the dose does not exceed the highest dose safely administered in first-in-human study or healthy volunteer 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]

There is a potential risk that multiple doses of LOXO-305 may lead to decreases in white blood cells including neutrophils, lymphocytes, monocytes, and eosinophils. Therefore, to mitigate any potential immunosuppressive risks during the ongoing SARS-CoV-2 (COVID-19) pandemic, subjects will remain in the Clinical Research Unit (CRU) for 96 hours postdose (Day 23) to allow for LOXO-305 elimination. In addition, subject's hematology laboratory results will be reviewed prior to discharge from the CRU. 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 dose of caffeine, omeprazole, vitamin K, and warfarin administered in this study are not anticipated to induce any potential risk or benefit to subjects participating in this study, as they are single doses administered according to the dosing recommendations in the full prescribing information.

The safety monitoring practices employed will include AE reporting, vital sign measurements, 12-lead ECGs, clinical laboratory evaluations, and physical examinations, and are considered adequate to protect the subjects' safety.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of the study is to assess the effect of multiple oral doses of LOXO-305 on the PK of single oral doses of caffeine (CYP1A2 substrate), S-warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) in healthy subjects.

2.1.2. Secondary Objective

The secondary objective of the study is to assess the safety and tolerability of multiple oral doses of LOXO-305 when administered alone, and coadministered with a single oral dose of probe drug cocktail.

2.2. Endpoints

2.2.1. Primary Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of caffeine/paraxanthine, omeprazole, S-warfarin, and LOXO-305 (as appropriate):

- AUC_{0-24}
- AUC from hour 0 to the last measurable concentration (AUC_{0-t})
- AUC from hour 0 extrapolated to infinity (AUC_{0-inf})
- percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$)
- apparent systemic clearance (CL/F)
- apparent plasma terminal elimination half-life ($t_{½}$)
- C_{max}
- t_{max}
- apparent terminal elimination rate constant (λ_z)
- apparent volume of distribution at the terminal phase (V_z/F)
- mean residence time (MRT)
- AUC_{0-24} and AUC_{0-48} ratio of paraxanthine to caffeine (MRAUC; caffeine/paraxanthine only).

2.2.2. Secondary Endpoints

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 1, open-label, 2-period, fixed-sequence DDI study to investigate the effect of multiple oral doses of LOXO-305 on the PK of single oral doses of caffeine (CYP1A2 substrate) and its metabolite paraxanthine, S-warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) in healthy subjects.

In Period 1, Day 1, 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg vitamin K (tablets), will be administered in the morning following a fast of at least 10 hours predose and 2 hours postdose. Blood samples for concentrations of the substrates (caffeine/paraxanthine, omeprazole, and S-warfarin) in plasma will be collected CCI . Of the samples collected for concentrations of each substrate in plasma CCI , samples will be analyzed for concentration of caffeine/paraxanthine from CCI , for concentration of omeprazole from CCI , and concentrations of S-warfarin from CCI .

There will be a washout period of 5 days between administration of the probe drug cocktail on Day 1 and the first dose of LOXO-305 on Day 6.

In Period 2, on Days 6 through 19, oral doses of 200 mg LOXO-305 will be administered QD for 14 consecutive days in the morning at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour). On Day 15, LOXO-305 will be coadministered with 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg of vitamin K (tablets) at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour) following a fast of at least 10 hours predose and 2 hours postdose. On Days 7 through 11, and Days 13, 14, 16, 18, and 19, subjects will fast for at least 2 hours predose and 1-hour postdose. On Days 6, 12, and 17 where clinical laboratory evaluations are performed, subjects will fast for at least 8 hours predose and 1 hour postdose. Blood samples for concentrations of LOXO-305 in plasma will be collected and analyzed CCI . Blood samples for concentrations of the substrates (caffeine/paraxanthine, omeprazole, and S-warfarin) in plasma CCI . Of the samples collected for concentrations of each substrate in plasma predose CCI , samples will be analyzed for concentration of caffeine/paraxanthine CCI , for concentration of omeprazole CCI , and for concentration of S-warfarin CCI .

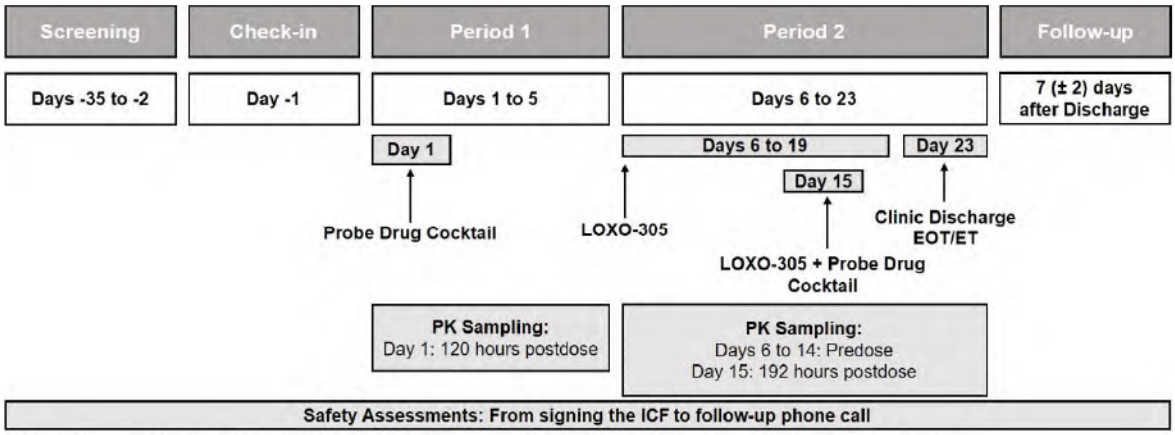
The schematic of the study design is displayed in Figure 3. The start of the study is defined as the date the first subject who is enrolled in the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned to receive a dose of study drug; this definition excludes screen failure subjects. Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects who are determined to be screen failures are permitted to be re-screened if the Investigator (or designee), with agreement from the Sponsor, feels that the subject may meet eligibility criteria upon re-screen. Re-screened subjects will be provided a new subject number.

To assess their eligibility to enter the study, potential subjects will be screened within 34 days (Days -35 to -2) and be admitted to the CRU on Day -1 (Check-in).

Subjects will be confined at the CRU from the time of Check-in (Day -1) until EOT on Day 23 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Dosing of probe drug cocktail will occur on Day 1 and Day 15 and dosing of LOXO-305 will occur on Days 6 through 19. 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 duration of participation is expected to be approximately 67 days (Screening through follow-up phone call).

Figure 3: Study Schematic



Abbreviations: EOT = End of Treatment; ET = Early Termination; ICF = Informed Consent Form; PK = pharmacokinetic.

In this study, physical examinations, 12-lead ECGs, vital sign measurements, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, hematology panel, 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 serious adverse events (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.

A Schedule of Assessments is presented in Appendix 4. Study completion is defined as the time of the last subject's follow-up phone call.

3.2. Discussion of Study Design

Metabolic routes of elimination, including most of those occurring through the CYP family of enzymes, can be inhibited or induced by concomitant drug treatment. Changes arising from metabolic DDI can be significant and contribute to increases or decreases in the blood and tissue concentrations of the parent drug or active metabolite. Increased or decreased concentrations of a parent drug or its metabolites can alter the safety and efficacy profile of a drug.

The probe drugs chosen in this study allow investigation of DDIs mediated through CYP450 enzymes. LOXO-305 showed no detectable inhibition (IC50 CCI µM) of CYP1A2, CYP2B6, and CYP2D6 and showed weak inhibition of CYP2C8, CYP2C9, CYP2C19, and CYP3A4. In vitro LOXO-305 induced CYP3A4, CYP2C19, and CYP2B6 and down regulated CYP1A2. The probe drugs were chosen as they are known to be sensitive substrates of CYP1A2 (caffeine), and CYP2C9 (warfarin), and CYP2C19 (omeprazole). Vitamin K will be administered with warfarin to counteract its anticoagulant effect.

The fixed single-sequence design used in this study is typical for drug interaction studies, because it allows intra-subject comparisons. A single sequence will be used to avoid carry over effects. This study will be open-label because the primary endpoints are not considered subjective.

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

Multiple oral doses of 200 mg LOXO-305 QD will be administered on Days 6 through Day 15 to achieve LOXO-305 steady state, ensuring the maximal effect of LOXO-305 when coadministered with the probe drug cocktail on Day 15. LOXO-305 200 mg QD will continue on Day 16 through Day 19 to maintain steady state of LOXO-305. While doses of 25 mg QD to 300 mg QD have been evaluated, LOXO-305 200 mg given QD has been chosen as the RP2D for the ongoing global Phase 1/2 first-in-human study, LOXO-BTK-18001 in patients with previously treated CLL/SLL or NHL. The available data demonstrate that LOXO-305 appears safe and well tolerated at these doses. At all evaluated doses, no dose-limiting toxicities have been identified in humans.[1]

3.3.2. Probe Drug Cocktail

The selected doses of the probe drugs caffeine, omeprazole, and warfarin were based on typical doses for these drugs when they are used as index substrates in DDI studies, and are considered to be high enough to provide sufficient plasma concentrations to achieve the

objectives of the study. The reason for the administration of the dose of vitamin K selected is to overcome the anti-coagulant effects of warfarin based on typical doses used for DDI studies.

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 35 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. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.3.4)
7. Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, and supine blood pressure [BP] and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.3.3)
8. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.3.1)
9. Clinical laboratory evaluations (Section 7.3.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
10. Screens for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV) immunoglobulin M (IgM) core antibody, human immunodeficiency virus (HIV) antibody, and COVID-19 via polymerase chain reaction (PCR) testing or equivalent (Appendix 2)
11. Hemoglobin A1c (HbA1c) test (Appendix 2)
12. Urine drug screen for selected drugs of abuse (including cotinine) and alcohol screen (breath or urine; Appendix 2)
13. Estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (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)
17. Blood sample for genotyping (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. Complete physical examination (Section 7.3.5)
5. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.3.4)
6. Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, and supine BP and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.3.3)
7. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.3.1)
8. Clinical laboratory evaluations (Section 7.3.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
9. Screen for COVID-19 via PCR test (or equivalent; Appendix 2)
10. Urine drug screen for selected drugs of abuse (including cotinine) and alcohol screen (breath or urine; Appendix 2)
11. eGFR calculated using the CKD-EPI equation (Appendix 2)
12. Serum pregnancy test (for female subjects only; Appendix 2)
13. 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 Check-in (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 Check-in (Day -1). 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 sign 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 Day 1) 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 consistent with post-menopausal status per the laboratory's reference ranges. 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). Female subjects are required to refrain from donation of ova from Check-in (Day -1) until 6 months after Day 19 (or last administration of study drug if subject terminates from the study early).

5. Male subjects who are capable of fathering a child must agree to use 1 of the following methods of contraception:
    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), or
    b. If documentation of surgical sterilization is not available, male subjects must follow 1 of the contraception methods below from Day 1 through 6 months after Day 19 (or last administration of study drug if subject terminates from the study early):
        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®); or
            2. established use of oral, implanted, injected, transdermal, intravaginal, or hormonal method of contraception associated with inhibition of ovulation; or
            3. 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 Day 1 for male partner); or
            4. be post-menopausal with amenorrhea for at least 1 year prior to Day 1 and FSH serum levels consistent with post-menopausal 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 from Check-in (Day -1) through 6 months after Day 19 (or last administration of study drug if subject terminates from the study early), 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 from Check-in (Day -1) through 6 months after

Day 19 (or last administration of study drug if subject terminates from the study early), unless the male subject uses a condom with spermicide. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after Day 19 (or last administration of study drug if subject terminates from the study early).

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 23-night stay at the CRU and follow-up phone call.

4.4. Exclusion Criteria

The following will exclude potential subjects from the study:

1. History or presence of any of the following, deemed clinically significant by the Investigator (or designee), and/or Sponsor:
    a. liver disease
    b. pancreatitis
    c. peptic ulcer disease
    d. intestinal malabsorption
    e. cholecystectomy
    f. gastric reduction surgery
    g. history or presence of clinically significant cardiovascular disease:
        i. myocardial infarction or cerebrovascular thromboembolism within 6 months prior to Day 1
        ii. symptomatic angina pectoris within 6 months prior to Day 1
        iii. congestive heart failure ≥ stage 2 per New York Heart Association Classification within 6 months prior to Day 1
        iv. congenital prolonged QT syndrome
        v. ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        vi. arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention within 6 months prior to Day 1
        vii. ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)
        viii. ECG abnormalities that are clinically significant at Screening, Check-in (Day -1), or predose on Day 1, including, but not limited to:
            1. complete left bundle-branch block

2. second-degree atrioventricular (AV) block, type 2, or third-degree AV block
3. QT interval corrected for heart rate (HR) using Fridericia's method (QTcF) > 450 msec

   Subjects with out-of-range ECG values or abnormal ECG findings that are not clinically significant will be permitted to have ECGs repeated up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 to confirm eligibility for study participation, if the repeat value(s) are normal/fall outside of the ranges stated above.

2. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital sign measurements at Screening, Check-in (Day -1), or prior to dosing on Day 1. Out-of-range vital sign measurements are defined as:
   a. body temperature > 37.5°C;
   b. pulse rate < 50 or > 99 beats per minute (bpm);
   c. systolic BP < 89 or > 139 mmHg;
   d. diastolic BP < 50 or > 89 mmHg;
   e. oxygen saturation < 95% (room air).

   Subjects with out-of-range values for these parameters that are not clinically significant will be permitted to have vital sign measurements repeated up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 to confirm eligibility for study participation if the repeat value(s) are normal/fall outside of the ranges stated above.
3. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator (or designee), or mentally or legally incapacitated or has significant emotional problems at the time of the Screening visit or expected during the conduct of the study.
4. Clinically significant abnormality, as determined by the Investigator (or designee), from physical examination at Check-in (Day -1).
5. Abnormal laboratory values (hematology panel, UA, clinical chemistry panel [fasted at least 8 hours]) that are clinically significant excluding those further defined in exclusion criteria #6, #7, and #8 at Screening and/or Check-in (Day -1). Subjects with out-of-range clinical laboratory results that are not clinically significant (excluding those further defined in exclusion criteria #6, #7, and #8) may have laboratory assessments repeated at the Investigator (or designee)'s discretion up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall within normal ranges or are stabilizing.
6. Abnormal liver function tests (LFTs) as defined by aspartate aminotransferase, alanine aminotransferase, and serum (total and direct) bilirubin, as well as amylase, or lipase above the upper limit of the normal range per the laboratory's reference ranges at Screening or Check-in (Day -1). Subjects with out-of-range LFTs, amylase, and lipase values above the upper limit of normal that are not clinically significant will be permitted to have LFTs, amylase, or lipase assessments repeated up to 2 times during

Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall within normal ranges.

7. Creatine kinase values above the upper limit of the normal range per the laboratory's reference ranges that are clinically significant at Screening or Check-in (Day -1). Subjects with out-of-range creatine kinase values that are not clinically significant will be permitted to have the creatine kinase assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) are stable or normalizing.
8. Estimated glomerular filtration rate (eGFR) $\leq$ 80 mL/minute/1.73m^2 calculated using the CKD-EPI equation at Screening or Check-in (Day -1). Subjects with out-of-range eGFR values that are not clinically significant will be permitted to have eGFR assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall above the range stated above.
9. HbA1c $\geq$ 6.5% at Screening. Subjects with out-of-range HbA1c values that are not clinically significant will be permitted to have HbA1c assessments repeated up to 2 times during Screening to confirm eligibility for study participation if the repeat value(s) fall below the range stated above.
10. Positive serologic test for HBsAg, HBV IgM core antibody, HCV antibody, or HIV antibody at Screening. Subjects who are positive for HBV IgM core antibody or HCV antibody require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HBV core antibody or HCV antibody positive or for whom a PCR is unable to be obtained will not be eligible.
11. Positive PCR test (or equivalent) for COVID-19 at Screening or Check-in (Day -1). Further details regarding COVID-19 testing (including procedures for subjects who test positive at any time throughout CRU confinement) are specified in a separate document.
12. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).
13. Significant history or clinical manifestation of any allergic, dermatological, biliary, hepatic, gastrointestinal, renal, metabolic, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or heart failure), neurological, or psychiatric disorder (as determined by the Investigator [or designee]), 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 appendectomy and/or hernia repairs will be acceptable.
14. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator (or designee), 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.
15. History of a major surgical procedure within 30 days prior to Screening.
16. Known ongoing alcohol and/or drug abuse within 2 years prior to Screening, or evidence of such abuse as indicated by the laboratory assays for drugs of abuse (including cotinine and alcohol) conducted during Screening and/or at Check-in

(Day -1). Tests for drugs of abuse must be negative at both Screening and Check-in (Day -1).

17. Use of tobacco, smoking-cessation products, or products containing nicotine and e-cigarettes (nicotine and non-nicotine), within 3 months prior to Screening and through EOT or ET.
18. 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 [including herbal products such as St. John's wort], CYP2C8 substrates, strong P-gp inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, vitamin supplements, caffeine [with the exception of caffeine administered for the purposes of this study/in accordance with the protocol], herbal products, natural or herbal supplements, and hormone-replacement therapy [HRT]) from 14 days prior to Day 1 or 5 half-lives (if known, whichever is longer [except for paracetamol/acetaminophen maximum of 2 g/day for up to 3 consecutive days during the study]) through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
19. 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.
20. Consumption of alcohol-containing foods or beverages or caffeine-containing foods or beverages (including but not limited to teas [including decaffeinated teas], coffees [including decaffeinated coffees], colas [including decaffeinated colas], energy drinks, gum containing caffeine, chocolate, and foods and beverages containing chocolate) within 72 hours prior to Check-in (Day -1) and through EOT or ET.
21. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
22. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator (or designee), within the 30 days prior to Day 1 and through EOT or ET.
23. 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 Day 1.
24. Has previously received LOXO-305 in any other study investigating LOXO-305, within 30 days prior to Day 1.
25. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET.
26. Poor peripheral venous access.
27. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
28. Receipt of blood products within 2 months prior to Check-in (Day -1).
29. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
30. Subject who are non- and slow CYP2C9 (CYP2C9 *2/*3 or CYP2C9 *3/*3 genotypes) and CYP2C19 (CYP2C19 *2/*2, CYP2C19 *2/*3, or CYP2C19 *3/*3 genotypes) metabolizers as determined by genotyping at Screening.

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).

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

If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced. Replacement subjects will be assigned a subject number by adding 200 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-301 replaces Subject Number 001-101).

Subjects who are determined to be screen failures are permitted to be re-screened if the Investigator (or designee), with agreement from the Sponsor, feels that the subject may meet eligibility criteria upon re-screen. Re-screened subjects will be provided a new subject number as defined above.

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
- non-compliance with study restrictions
- 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 Sponsor. In case of withdrawal, efforts will be made to perform all ET 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:

- AEs 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 LOXO-305. Covance will procure adequate quantities of caffeine, omeprazole, warfarin, and vitamin K (Table 2).

Table 2: Study Drugs

Study Drug	Form[a]	Strength	Supplier	Manufacturer[b]
LOXO-305	Tablet	2 × 100 mg	Loxo Oncology, Inc.	Catalent San Diego or Lonza Pharma & Biotech
Caffeine	Tablet	200 mg	McKesson	Meda Consumer Health
Omeprazole	Capsule	40 mg	McKesson	Sandoz
Warfarin	Tablet	10 mg	McKesson	Taro
Vitamin K	Tablets	2 × 5 mg	McKesson	Valeant Pharmaceuticals

[a] Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug(s).
[b] The manufacturer will be confirmed by the site at the time of drug procurement.

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 will be stored according to the instructions on the label.

The probe drug cocktail study drugs will be supplied by Covance, along with the lot numbers. The probe drug cocktail study drugs will be provided in high-density polyethylene bottles (omeprazole and warfarin) and blister packs (caffeine) and will be stored according to the instructions on the package insert.

Vitamin K tablets will be supplied by Covance, along with the lot numbers. The vitamin K tablets will be provided in high-density polyethylene bottles and will be stored according to the instructions on the package insert.

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

Subjects will receive each of the following treatments throughout the study:

- In Period 1, Day 1, 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) will be administered as a single dose of probe drug cocktail, along with 10 mg vitamin K (2 × 5 mg tablets), in the morning following a fast of at least

10 hours predose and 2 hours postdose. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose administration.

- In Period 2, on Days 6 through 19, oral doses of 200 mg (2 × 100 mg tablets) LOXO-305 will be administered QD for 14 consecutive days in the morning at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour). On Day 15, LOXO-305 will be coadministered with 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg vitamin K (2 × 5 mg tablets), at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour) following a fast of at least 10 hours predose and 2 hours postdose. On Days 7 through 11, and Days 13, 14, 16, 18, and 19, subjects will fast for at least 2 hours predose and 1 hour postdose. On Days 6, 12, and 17 where clinical laboratory evaluations are performed, subjects will fast for at least 8 hours predose and 1 hour postdose. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose 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. Water will be restricted for 1-hour predose and 1-hour postdose, with the exception of water administered for dose administration.

Each unit dose will be prepared by qualified CRU staff.

Appropriate unit dose(s), as described above, will be administered to subjects. Although the timing of events requires that each subject will be 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

This is a non-randomized study. The study has a fixed treatment sequence.

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 oral 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, caffeine, warfarin, vitamin K, and omeprazole will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of LOXO-305, caffeine, warfarin, and vitamin K tablets, and the 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 will be disposed of by the CRU, in accordance with the CRU's Standard Operating Procedures (SOPs) and local/state/federal guidelines governing waste disposal of investigational drugs, following the Sponsor's written authorization. The caffeine, warfarin, and vitamin K tablets and omeprazole capsules will be disposed of by the CRU in accordance with the CRU's SOPs.

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 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 Day 1.

All prescription medications and over-the-counter medications including but not limited to: moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers (including herbal products such as St. John's wort), CYP2C8 substrates, strong P-gp inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, herbal products, vitamin supplements, natural or herbal supplements, caffeine (with the exception of caffeine administered for the purposes of this study/in accordance with the protocol), and HRT are prohibited for 14 days or 5 half-lives (if known; except for paracetamol/acetaminophen as referenced above), whichever is longer, prior to Day 1 and through EOT or ET, unless deemed acceptable by the, Investigator (or designee), and Sponsor. 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 and e-cigarettes (nicotine and non-nicotine) 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.

Consumption of alcohol-containing foods or beverages or caffeine-containing foods or beverages (including but not limited to teas [including decaffeinated teas], coffees [including decaffeinated coffees], colas [including decaffeinated colas], energy drinks, gum containing caffeine, chocolate, and foods and beverages containing chocolate) within 72 hours prior to Check-in (Day -1) and through EOT or ET will not be allowed.

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

Fasting requirements and water restrictions 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 each substrate (caffeine/paraxanthine, omeprazole, and S-warfarin) and 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

Plasma concentrations of each substrate (caffeine/paraxanthine, omeprazole, and S-warfarin) and LOXO-305 will be determined using validated bioanalytical methods. Specifics of the bioanalytical methods will be provided in a separate document.

7.2. Genotyping

A blood sample for genotyping to exclude subjects who are non- and slow CYP2C9 (CYP2C9 *2/*3 or CYP2C9 *3/*3 genotypes) and CYP2C19 (CYP2C19 *2/*2, CYP2C19 *2/*3, or CYP2C19 *3/*3 genotypes) metabolizers will be collected at the Screening.

Blood volume required for genotyping is presented in Appendix 3.

7.3. 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 order of priority):

- dosing
- PK blood sampling
- vital sign measurements *
- 12-lead ECGs *
- blood and urine samples for clinical laboratory evaluations
- physical examination.

* When vital sign measurements and 12-lead ECGs are scheduled at the same time as PK blood sampling, the PK blood sampling will be obtained at the scheduled timepoint, and the

vital sign measurements followed by 12-lead ECGs will be obtained prior to and as close as possible to the scheduled PK blood sampling.

7.3.1. 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 sign measurement, 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 sign measurements, or clinical laboratory evaluations, 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 additional safety information.

7.3.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations (clinical chemistry panel [fasted at least 8 hours; at ET or the day before EOT, subjects are not required to be fasted prior to clinical laboratory evaluations], coagulation parameters, hematology panel, TSH [Screening only], HbA1c [Screening only], eGFR [Screening and Check-in (Day -1)], and UA) will be collected at the timepoints specified in Appendix 4.

Screens for HCV antibody, HBsAg, HBV IgM core antibody, and HIV antibody will be performed at Screening.

Testing for COVID-19 via PCR (or equivalent) will be performed at the timepoints specified in Appendix 4. Testing for COVID-19 may also be conducted periodically during the subject's CRU confinement, at the discretion of the Investigator (or designee). Further details regarding COVID-19 testing (including procedures for subjects who test positive at any time throughout CRU confinement) are specified in a separate document.

A urine drug screen for selected drugs of abuse (including cotinine) and an alcohol screen (urine or breath) 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 are presented in Appendix 3. A list of the specific evaluations is in Appendix 2.

7.3.3. Vital Signs

Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, 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 sign measurements are scheduled at the same time as PK blood draws, the PK blood draws will be obtained at the scheduled timepoint, and the vital sign measurements will be obtained prior to and as close as possible to the scheduled PK blood draw.

7.3.4. 12-lead Electrocardiogram

A 12-lead ECG (including HR, PR, RR, QRS, and QT interval parameters) will be obtained after the subject has been resting for at least 10 minutes in the supine position at the timepoints specified in Appendix 4. The QT interval will be corrected for HR by Fridericia's ($QTcF = QT/[RR]^{1/3}$) formula.

When 12-lead ECGs are scheduled at the same time as PK blood draws, the PK 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 PK blood draw.

7.3.5. 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

Up to 16 healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. The sample size chosen for this study was selected without statistical considerations but is consistent with previous studies of a similar design. Up to 16 subjects are anticipated to be sufficient to provide a reliable estimate of the magnitude and variability of the interaction. Replacement subjects may be enrolled only if deemed necessary by the Sponsor. Every attempt will be made to enroll at least 4 subjects of each sex in the study.

8.2. Analysis Populations

The **PK Population** will consist of all subjects who have received a dose of LOXO-305 or the probe cocktail drugs, 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 t_{max}. The impact of protocol deviations on the PK population will be evaluated on a case-by-case basis.

The **Safety Population** will consist of all subjects who have received at least 1 dose of study drug (probe cocktail drugs and/or LOXO-305). Subjects will be classified into groups based on actual treatment received.

8.3. Pharmacokinetic Analysis

Serial blood samples for plasma concentration analysis will be analyzed using samples collected at the following timepoints:

- Caffeine/paraxanthine:
  - CCI following administration alone on CCI
- Omeprazole:
  - CCI following administration alone on CCI
- S-Warfarin:
  - CCI following administration alone on CCI
- LOXO-305:
  - CCI following administration alone on CCI
  - CCI following administration with CCI

Whenever possible, the following PK parameters for each substrate (caffeine/paraxanthine, omeprazole, and S-warfarin) and LOXO-305 will be calculated for each subject based on the plasma concentrations (as appropriate):

- area under the concentration time curve (AUC) from hour 0 to 24 hours postdose (AUC_{0-24})
- AUC from hour 0 to the last measurable concentration (AUC_{0-t})
- AUC from hour 0 extrapolated to infinity (AUC_{0-inf})
- percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$)
- apparent systemic clearance (CL/F)
- C_{max}
- mean residence time (MRT)
- apparent plasma terminal elimination half-life ($t_{½}$) wherever possible, where $t_{1/2}$ = natural log (2)/λ_Z
- time to maximum observed plasma concentration (t_{max})
- apparent terminal elimination rate constant (λ_Z)
- apparent volume of distribution at terminal phase (V_Z/F)
- AUC_{0-24} and AUC_{0-48} ratio of paraxanthine to caffeine (MRAUC; caffeine/paraxanthine only)

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 analyses will be performed using SAS® Version 9.4 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).

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

8.3.2. Statistical Methodology

The primary analysis planned for this study is a mixed effect model that includes treatment as a fixed effect and subject as a random effect. The analysis will be performed on the natural log (ln)-transformed PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) and 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 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 will be probe drugs alone (caffeine and its metabolite paraxanthine, omeprazole, and S-warfarin) versus probe drugs (caffeine and its metabolite paraxanthine, omeprazole, and S-warfarin) coadministered with LOXO-305. The ratio of paraxanthine to caffeine will be summarized.

8.4. Safety Analysis

All safety assessments, including AEs, SAEs, vital sign 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 study drug on Day 1, Period 1. 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, September 2019). Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 (or higher). The incidence of AEs will be presented by severity and by relationship to study drug as determined by the Investigator or designee (Appendix 1 for AE reporting). All TEAEs will be summarized by system organ class and preferred term.

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 CRU staff member.

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 Sponsor-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 SOPs or per Sponsor 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 and/or 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(s) who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor(s) 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(s) will visit the CRUs at suitable intervals (or may perform activities remotely as per the Monitoring Plan for this study) and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor(s) 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(s) 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(s), 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), and Investigational New Drug Application (21 CFR 312), as appropriate. As such, these sections of US Title 21 CFR, along with the

applicable ICH Guidelines, are commonly known as Good Clinical Practices, which are consistent with the Declaration of Helsinki.

9.9. Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

10. REFERENCES

1. Loxo Oncology, Inc. LOXO-305 - Investigator's Brochure (Version 4.0). 29 October 2020.

2. Brandhuber B, Gomez E, Smith S, Eary T, Spencer S, Rothenberg SM, et al. A next generation reversible BTK Inhibitor, for overcoming acquired resistance to irreversible BTK inhibitors. Clin Lymphoma Myeloma Leuk. 2018;18; S216.

3. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013 Jul 4;369(1):32–42.

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. Woyach J, Huang Y, Rogers K, Bhat SA, Grever MR, Lozanski A, et al. Resistance to acalabrutinib in CLL is mediated primarily by BTK mutations. Blood. 2019;134(Supplement_1).

6. 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.

7. 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.

8. Toyoshima S, Kanno A, Kitayama T, Sekiya K, Nakai K, Haruna M, et al. QT PRODACT: In Vivo QT Assay in the Conscious Dog for Assessing the Potential for QT Interval Prolongation by Human Pharmaceuticals [Internet]. Journal of pharmacological sciences. 2005 [cited 2020 Jun 10]. Available from: https://pubmed.ncbi.nlm.nih.gov/16493187/

9. Food and Drug Administration. Guidance for Industry: Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry [Internet]. Food and Drug Administration; 2020 [cited 2020 Sep 25]. Available from: https://www.fda.gov/media/134581/download

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 starts on or after the first administration of study drug.

The following are all AEs:

- unfavorable changes in general condition
- subjective or objective signs/symptoms
- concomitant diseases or accidents
- clinically significant 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 End of Study (EOS) or Early Termination (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 on Day 19 (or last administration of study drug if subject terminates from the study early) 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 (or designee) 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 (or designee) until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator (or designee) should notify Covance or the Sponsor's Clinical Safety Representative. At the completion of the pregnancy, the Investigator (or designee) 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 (or designee) should follow the procedures for reporting an SAE.

Male subjects will be instructed to notify the Investigator (or designee) 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 Clinical Research Unit (CRU) becomes aware that the female partner of a male subject is pregnant, they are to contact the Investigator (or designee) 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 Case Report Form (eCRF; as appropriate), in addition to completion of the required pregnancy forms. If the Investigator (or designee) 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 the 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 1 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 1 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

The FDA-reportable AEs are AEs that are associated with the use of the drug and represent events that are assessed as serious, related, and unexpected. The FDA-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):	Hematology Panel:	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 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] Estimated glomerular filtration rate[a,d] SARS-CoV-2 (COVID-19) test
		Coagulation Parameters:
		Partial thromboplastin time Prothrombin time International normalized ratio
		Serology:[b]
		Hepatitis B surface antigen (HBsAg) Hepatitis B virus (HBV) immunoglobulin M (IgM) core antibody Hepatitis C virus (HCV) antibody Human immunodeficiency virus (HIV) antibody
	Urinalysis:	**For Female Subjects Only:**
Urine Drug Screen:[a]	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 occult blood is positive)	Pregnancy test (serum qualitative, serum quantitative may be used for confirmation if needed)[c] Follicle-stimulating hormone (post-menopausal female subjects only)[b]
Including but not limited to the following: Alcohol (ethanol)[e] Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine (metabolite) Methadone Opiates Phencyclidine Cotinine		

a. Performed at Screening and Check-in (Day -1) only.
b. Performed at Screening only.
c. Performed at Screening, Check-in (Day -1), and Day 22 for End of Treatment (EOT) or Early Termination (ET) only.
d. Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
e. Urine or breath test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject:

Assessment	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	8.0	1	8.0
Hemoglobin A1c (HbA1c)	4.0	1	4.0
Probe drug cocktail pharmacokinetic (PK) sampling[a]	4.0	36	144.0
LOXO-305 PK sampling	4.0	30	120.0
Clinical laboratory evaluations: Hematology Clinical chemistry[b] Coagulation	 4.0 4.0 3.0	 9 9 9	99.0
Serum pregnancy test (female subjects only)	4.0	3	12.0
Serum follicle-stimulating hormone (post- menopausal female subjects only)	4.0	1	4.0
Genotyping	14.0	1	14.0
		Total:	**405.0 mL**

[a] For PK samples for analysis of each substrate (caffeine/paraxanthine, omeprazole, and S-warfarin) a single blood sample will be collected.
[b] Thyroid-stimulating hormone (TSH) and estimated glomerular filtration rate (eGFR) will be assessed as part of the clinical chemistry sample.

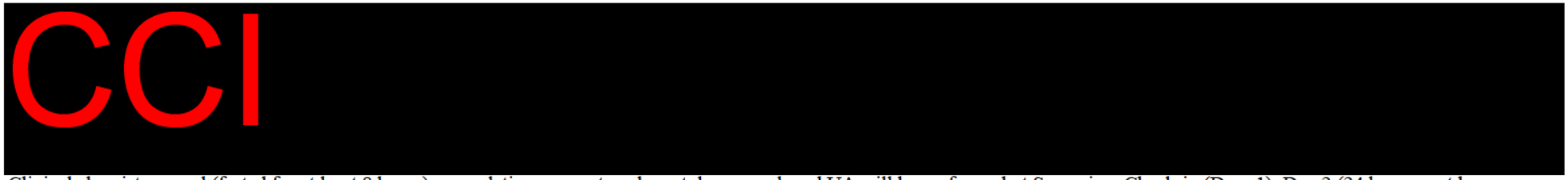
If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Schedule of Assessments

Study Procedures[a]	Screening (Days -35 to -2)	Check-in (Day -1)	Period 1					Period 2																	Clinic Discharge EOT/ET[u]	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	7 (± 2) days post EOT/ET[v]
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	
Inclusion/Exclusion Criteria	X	X																								
Informed Consent	X																									
Demographics	X																									
Medical History	X	X[b]																								
Height/Weight/BMI	X	X[c]																								
eGFR	X	X																								
Genotyping	X																									
Physical Examination[d]		X																							X	
12-lead ECG[e]	X	X	X				X	X						X			X		X			X			X	
Vital Sign Measurements[f,g,h]	X	X	X				X	X						X			X		X			X			X	
HDYF? Inquiry[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
AEs/SAEs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X
Probe Drug Cocktail Dosing[k]			X														X									
LOXO-305 Dosing[l]								X	X	X	X	X	X	X	X	X	X	X	X	X	X					
CCI																										
Clinical Laboratory Evaluations[o]	X	X		X				X						X			X		X			X		X	X	
Hepatitis and HIV Screen	X																									
COVID-19 Test[p]	X	X																								
HbA1c Test	X																									
Drug Screen[q]	X	X																								
Prior and Concomitant Medications[r]	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[s]	X	X																						X	X	
FSH Test[t]	X																									
TSH Test	X																									

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; COVID-19 = SARS-CoV-2; CRF = Case Report Form; CRU = Clinical Research Unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; 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. Height collected at Screening only; BMI calculated based on Screening height.
d. A complete physical examination will be performed at Check-in (Day -1). An abbreviated physical examination will be performed at Day 23 (EOT) or at ET.
e. 12-lead ECGs will be obtained at Screening and Check-in (Day -1), Day 1 (predose), Day 5 (96 hours postdose on Day 1), Day 6 (predose and 2 hours postdose), Day 12 (predose), Day 15 (predose and 2 hours postdose), Day 17 (predose), and Day 20 (24 hours postdose on Day 19), and Day 23 (96 hours postdose on Day 19 [EOT]) or ET. 12-lead ECGs will be collected after the subject has rested in the supine position for at least 10 minutes. When scheduled at the same time as PK blood draws, 12-lead ECGs will be obtained prior to and as close as possible to having blood drawn. The allowed sampling window for 12-lead ECGs is ± 30 minutes from the nominal timepoint for all postdose 12-lead ECGs and no less than 10 minutes prior to dosing for predose 12-lead ECGs.
f. Vital sign measurements (supine BP and pulse rate) will be obtained at Screening, Check-in (Day -1), Day 1 (predose), Day 5 (96 hours postdose on Day 1), Day 6 (predose and 2 hours postdose), Day 12 (predose), Day 15 (predose and 2 hours postdose), Day 17 (predose), and Day 20 (24 hours postdose on Day 19), and Day 23 (96 hours postdose on Day 19 [EOT]) or ET. 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. When scheduled at the same time as PK blood draws, vital sign measurements should be carried out prior to and as close as possible to having blood drawn. The allowed sampling window for vital sign measurements is ± 30 minutes from the nominal timepoint for all postdose vital sign measurements and no less than 10 minutes prior to dosing for predose vital sign measurements.
g. Respiratory rate and body temperature will be obtained at Screening, Check-in (Day -1), and Day 23 (96 hours postdose on Day 19 [EOT]) or ET.
h. Oxygen saturation will be measured via pulse oximetry at Screening, Check-in (Day -1), predose on Day 1, and Day 23 (96 hours postdose on Day 19 [EOT]) or ET. The allowed sampling window for oxygen saturation measurements is ± 30 minutes from the nominal timepoint for all postdose oxygen saturation measurements and no less than 10 minutes prior to dosing for predose oxygen saturation measurements.
i. A HDYF? inquiry will be performed at Screening (after the ICF is signed), at Check-in (Day -1), at each postdose vital sign measurement, and at an appropriate time for all other days.
j. 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.
k. On Day 1 and Day 15, the probe drug cocktail (200 mg caffeine [tablet], 40 mg omeprazole [capsule], and 10 mg warfarin [tablet]) and 10 mg vitamin K (tablets) will be administered orally in the morning following a fast of at least 10 hours prior to dosing and 2 hours postdose (with water restricted for 1 hour prior to and 1 hour postdose administration).
l. On Day 6 through Day 19, oral doses of 200 mg LOXO-305 will be administered QD in the morning at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour). On Days 7 through 11, and Days 13, 14, 16, 18, and 19, subjects will be fasted for at least 2 hours predose and 1 hour postdose. On days where clinical laboratory evaluations are performed (Day 2, Day 6, Day 12, and Day 17) subjects will be fasted for 8 hours predose and 1 hour postdose. On Day 15, 200 mg LOXO-305 will be coadministered with probe drug cocktail (200 mg caffeine [tablet], 40 mg omeprazole [capsule], and 10 mg warfarin [tablet]) and 10 mg vitamin K (tablets) in the morning at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour), following a fast of 10 hours prior to dosing and 2 hours postdose (with water restricted for 1 hour prior to and 1 hour postdose).
m. CCI [redacted]

n. 

o. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and UA will be performed at Screening, Check-in (Day -1), Day 2 (24 hours postdose on Day 1), Day 6 (predose), Day 12 (predose), Day 15 (predose), Day 17 (predose), Day 20 (24 hours postdose on Day 19), and Day 22 (72 hours postdose on Day 19, if the subject completes the study [EOT]), or on the day of ET. At ET or the day before EOT (Day 22), subjects are not required to be fasted prior to clinical laboratory evaluations.
p. Testing for COVID-19 will be conducted at a minimum at Screening and Check-in (Day -1). Testing for COVID-19 may also be conducted periodically during the subject's CRU confinement, at the discretion of the Investigator (or designee). Tests will be performed by rapid polymerase chain reaction or equivalent.
q. Urine drug screen for drugs of abuse (including cotinine) and alcohol screen (urine or breath).
r. Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved prescription and over-the-counter medications taken by a subject within 14 days or 5 half-lives (if known), whichever is longer, prior to Day 1 will be recorded on the subject's electronic CRF.
s. Female subjects only. Performed at Screening, Check-in (Day -1), and Day 22 (72 hours postdose on Day 19), if the subject completes the study (EOT) or on the day of ET.
t. Post-menopausal female subjects only.
u. End of Treatment is defined as when the subject is released from the CRU following completion of all assessments through Day 23. Early Termination is defined as when the subject is released from the CRU if the subject terminates the study early. Vital sign measurements, ECG, and abbreviated physical examination results are to be available for review by the Investigator (or designee) prior to subject release from the CRU on Day 23 (EOT) or ET. Clinical laboratory results (for clinical chemistry, hematology, coagulation, and UA) and serum pregnancy test results (female subjects only) are to be available for review by the Investigator (or designee) prior to subject release from the CRU at the EOT visit and prior to subject release from the CRU at the ET visit if available.
v. To be conducted 7 days (± 2 days) following EOT or ET. End of Study is defined as when the subject is contacted by the CRU for 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 or probe drug cocktail (including subjects who are terminated early) will receive a follow-up phone call.
w. Denotes predose sample collection only.