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A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

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Protocol

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

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

Sponsor Signatory:
PPD

Principal Investigator:
PPD

SPONSOR APPROVAL

I have read the protocol and approve it:

04-Aug-20 | 12:09:58 PDT

Date

INVESTIGATOR AGREEMENT

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

PPD

04AUG2020
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 PPD 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 (SAE) Reporting	Email: SAEIntake@covance.com
Study Site	Covance Clinical Research Unit (CRU), Inc. 1900 Mason Avenue, Suite 140 Daytona Beach, Florida 32117 USA
Principal Investigator	PPD PPD Covance Clinical Research Unit Inc. 1900 Mason Avenue, Suite 140 Daytona Beach, Florida 32117 USA Tel: PPD Fax: PPD
Sub-investigator(s)	Obtain information from Form FDA 1572
Clinical Laboratory	LabCorp - Hollywood 4200 North 29th Avenue Hollywood, Florida 33020 USA
Bioanalytical Laboratory	Alturas Analytics, Inc. 1324 Alturas Drive Moscow, Idaho 83843 Tel (main): PPD Email: PPD

Statistician	PPD Covance Tel: PPD Email: PPD
Protocol Medical Writer	PPD Covance Tel: PPD Email: PPD

SYNOPSIS

Study Title

A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

Objectives

The primary objective of the study is:

- To assess the safety and tolerability of single oral doses of LOXO-305 when administered to healthy adult subjects.

The secondary objective of the study is:

- To assess the pharmacokinetics (PK) of single oral doses of LOXO-305 when administered to healthy adult subjects.

Study Design

This is an open-label, single-ascending dose study to evaluate the safety, tolerability, and PK of LOXO-305.

Up to 4 cohorts are planned for evaluation. In each cohort, 6 healthy adult subjects are planned for evaluation. Subjects will participate in only 1 cohort. In each cohort, subjects will receive a single oral dose of LOXO-305 on Day 1. In each cohort, a sentinel group of 2 subjects will be dosed at least 48 hours before the remaining 4 subjects in the cohort (following review of available safety data). Blood samples will be collected for the PK assessment of LOXO-305 in plasma for 168 hours postdose.

A single oral dose of LOXO-305 will be administered on Day 1 for each cohort as follows:

- Cohort 1 (Treatment A): 300 mg
- Cohort 2 (Treatment B): up to 600 mg
- Cohort 3 (Treatment C): up to 900 mg

One additional cohort (6 subjects) may be enrolled if it is deemed appropriate to repeat any dose level, or to add an interim dose level or levels (equal to or lower than 900 mg), as determined by the Sponsor in consultation with the Investigator (or designee), depending on the safety, tolerability, and PK results from the prior cohort(s). Dosing will not exceed 900 mg in any subject, nor will any subject be given a dose for which the maximum observed plasma concentration (C_{max}) would exceed CCI ng/mL.

Dose escalation to a higher dose level (ie, next cohort) will not take place until the Investigator (or designee) and the Sponsor have reviewed all pertinent safety/tolerability data (ie, physical examinations, electrocardiograms [ECGs], vital sign measurements, clinical laboratory evaluations, and adverse events [AEs]) through a minimum of 168 hours (Day 8) and have determined that adequate safety and tolerability from the previous lower dose

cohort has been demonstrated to permit proceeding to the next cohort. Pharmacokinetic data through at least 72 hours (approximately 3 half-lives) will be reviewed to guide the dose-escalation decision. Data from a minimum of 4 subjects will be reviewed in order to make a dose escalation decision.

\To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 8 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. A follow-up phone call will occur for all subjects who received 1 dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET.

Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

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

In this study, physical examinations, 12-lead ECGs, vital sign measurements, PK sampling, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, hematology panel, urinalysis (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 AEs (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.

Number of Subjects

The study is planned to enroll up to 24 healthy adult male and female subjects (women of non-childbearing potential only). Six subjects will participate in each cohort.

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives.

Every attempt will be made to enroll at least 1 subject of each sex in each cohort in the study.

Main Criteria for Inclusion

Male subjects and female subjects of non-childbearing potential, between 18 and 55 years of age, inclusive, at Screening, and within body mass index range 18.0 to 32.0 kg/m^2, inclusive. Subjects will be in good general health, based on medical history, physical examination findings, vital sign measurements, 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

LOXO-305 will be supplied by the Sponsor as 25-mg tablets. Light blue opaque size 0 capsules will be supplied by Covance. LOXO-305 tablets will be over-encapsulated into light blue opaque size 0 capsules (4 tablets per capsule) by Covance for oral administration.

Cohort 1 (Treatment A):

- A single oral dose of 300 mg LOXO-305 (12 × 25-mg tablets, over-encapsulated [3 capsules]) following a fast of at least 10 hours prior to and 4 hours after dosing.

Cohort 2 (Treatment B):

- A single oral dose of up to 600 mg LOXO-305 (24 × 25-mg tablets, over-encapsulated [6 capsules], or less depending on the dose chosen) following a fast of at least 10 hours prior to and 4 hours after dosing.

Cohort 3 (Treatment C):

- A single oral dose of up to 900 mg LOXO-305 (36 × 25-mg tablets, over-encapsulated [9 capsules], or less depending on the dose chosen) following a fast of at least 10 hours prior to and 4 hours after dosing.

One additional cohort (6 subjects) may be enrolled if it is deemed appropriate to repeat any dose level, or to add an interim dose level or levels (equal to or lower than 900 mg), as determined by the Sponsor in consultation with the Investigator (or designee), depending on the safety, tolerability, and PK results from the prior cohort(s). Dosing will not exceed 900 mg in any subject, nor will any subject be given a dose for which the C_{max} would exceed CCI ng/mL.

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

Duration of Subject Participation in the Study:

Planned Enrollment/Screening Duration: Approximately 28 days (Days -29 to -2).

Length of Confinement: Up to 9 days (Days -1 to 8).

Planned Study Conduct Duration: Up to 46 days (Screening through follow-up call).

Criteria for Evaluation:

Pharmacokinetics:

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

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

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

Safety:

Safety will be monitored with AE inquiries, clinical laboratory evaluations, vital sign measurements, ECGs, concomitant medications, and physical examinations.

Statistical Methods:

Pharmacokinetics:

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).

Pharmacokinetic dose proportionality will be assessed for Cohort 1, 2, and 3. Natural log-transformed AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, and C_{max} of LOXO-305 will be evaluated using a power model of the form: $ln(parameter) = intercept + slope \times ln(dose) + random\ error$

For each PK parameter separately, a pooled estimate (across all doses) of slope, corresponding 95% confidence interval, and between-subject CV% will be calculated.

Safety:

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

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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve from time 0 extrapolated to infinity
ADL	Activities of Daily Living
AE	adverse event
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 time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
AV	atrioventricular
BID	twice daily
BMI	body mass index
BP	blood pressure
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CK	creatine kinase
CL/F	apparent systemic clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
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
HIV	human immunodeficiency virus
HRT	hormone-replacement therapy
IB	Investigator's Brochure
IC_{90}	concentration required for 90% inhibition

ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LFT	liver function test
Ln	natural log
MedDRA	Medical Dictionary for Regulatory Activities
NHL	non-Hodgkin lymphoma
NOEL	no observed effect level
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)
SAE	serious adverse event(s)
SAP	Statistical Analysis Plan
SDD	spray-dried dispersion
SOC	system organ class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	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/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 (IMP), 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] 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] These features enable LOXO-305 dosed orally at 100 mg and higher once daily (QD) to achieve pharmacokinetic (PK) exposures that exceed the concentration required for 90% inhibition (IC_{90}) of BTK-wt and BTK C481 at trough and thus deliver tonic BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. LOXO-305 is also a highly selective molecule, with more than 300-fold more selectivity for BTK versus 370 other kinases tested and 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 binding site of the BTK competitively, with no evidence of irreversible binding.

1.2. Non-clinical Pharmacokinetics

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 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 cloned 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% inhibition for the inhibitory effects of LOXO-305 on hERG potassium currents was CCI µM, which is approximately CCI higher than the maximum unbound concentration of LOXO-305 in patients treated with the dose of 200 mg 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 CCI ng/mL, which is approximately CCI above the predicted C_{max} plasma LOXO-305 concentration (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.

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 rat at doses up to and including a dose of CCI mg/kg. The C_{max} at the no observed effect level (NOEL) 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. 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 or non-Hodgkin lymphoma (NHL). The starting dose of LOXO-305 was 25 mg QD.

As of 09 April 2020, safety data were available from 172 treated patients, with 300 mg QD as the highest dose administered (Section 1.3.1). As of 30 March 2020 (data cutoff date), PK data were available from 107 patients (Section 1.3.2). LOXO-305 was recently investigated in 1 study in healthy volunteers (LOXO-BTK-20014). LOXO-BTK-20014 is a pilot food-effect cross-over 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. A second study is ongoing in healthy volunteers (LOXO-BTK-20006), which is a drug-drug interaction 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 protocol development, 3 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days (one of which was co-administered with itraconazole), each followed by a wash out period.

1.3.1. Safety

As of 09 April 2020, 172 patients were treated in the first-in-human study (LOXO-BTK-18001) and received LOXO-305 at doses ranging from 25 mg QD to 300 mg QD. A full summary of treatment-emergent adverse events (TEAEs) for patients in this study is provided in the LOXO-305 IB and the Investigator is directed to the safety information described in that document.[1]

Overall, TEAEs were reported in 123 of 172 treated patients in the safety population and were mild or moderate severity (Grade 1 or 2) in 89 of 123 (51.7%) patients and were Grade 3 or 4 in severity in 33 of 123 (19.2%) patients. The most frequently reported TEAEs occurring in ≥ 10% of patients were fatigue (12.8% total, 7.0% related) and diarrhea (10.5% total, 6.4% related). The most frequently reported drug-related TEAEs (those in > 5% of patients) were fatigue (7.0%), diarrhea (6.4%), and contusion (5.2%). All other drug-related TEAEs occurred in < 5% of patients each. The most frequently reported Grade ≥ 3 TEAEs included neutropenia (4.1% total; 2.9% related), neutrophil count decreased (2.3% total; 1.2% related), anemia (1.7% total; 0.6% related), fatigue and platelet count decreased (each 1.2% total; each 0.6% related), and hypokalemia (1.2% total; none related).

Five patients (2.9% of all 172 patients treated) discontinued LOXO-305 because of TEAEs; 2 of the 5 patients (1.2% of all patients treated) discontinued LOXO-305 because of a treatment-related event. One of these patients with mantle cell lymphoma treated in the 100 mg QD group discontinued due to Grade 3 leukocytosis considered related to study drug. Study therapy was held for resolution of leukocytosis and the patient subsequently progressed and study therapy was not resumed; the event of leukocytosis was recorded as recovered/resolved. The second patient treated in the 150 mg QD group discontinued due to Grade 2 myalgia; the myalgia was ongoing. The patient had previously received ibrutinib which was discontinued after 3 months of treatment for AEs.

A total of 5 deaths have been reported for patients treated in this study, LOXO-BTK-18001. No deaths were considered related to LOXO-305.

From preliminary AE data reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20014 study, all TEAEs (headache, nausea, and vomiting) were Grade 1 in severity and considered related to LOXO-305. All 3 events were reported by 1 subject and resolved prior to End of Treatment (EOT; data on file at the time of protocol development). There were no AEs reported following LOXO-305 administration in 3 healthy volunteers in the LOXO-BTK-20006 study from preliminary data available (data on file at the time of protocol development).

1.3.2. Pharmacokinetics

As of March 30, 2020, PK data were available from 107 patients enrolled in LOXO-BTK-18001. Steady-state PK parameters of LOXO-305 in these cancer patients could be derived from data collected on Cycle 1 Day 8 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. Following administration of doses of 100 mg QD or higher, mean trough plasma levels of LOXO-305 exceeded the CCI of BTK in vitro (Figure 1).

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_{0-24} (ng*h/mL) Geo mean (%CV)	CL/F (L/h) Geo mean (%CV)	$t_{1/2}$ (h) Geo mean (%CV)
25 mg QD	CCI					
50 mg QD						
100 mg QD						

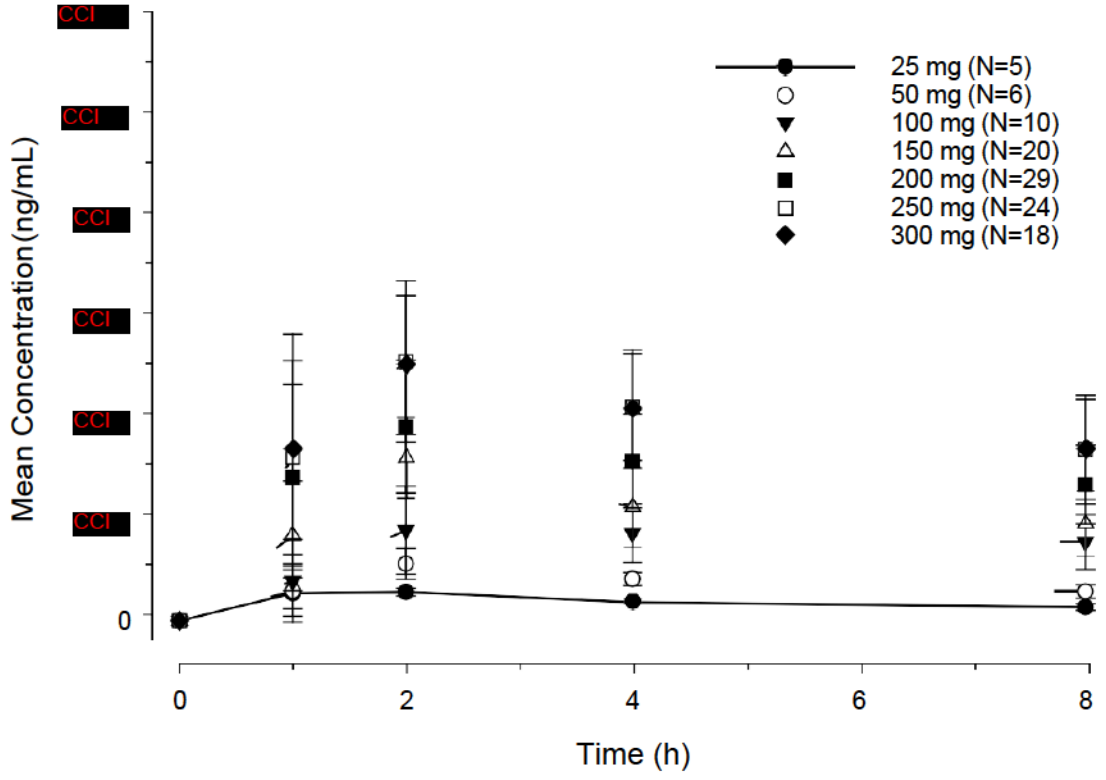
Dose Level	N	C_{max} (ng/mL) Geo mean (%CV)	T_{max} (h) Median (min, max)	AUC_{0-24} (ng*h/mL) Geo mean (%CV)	CL/F (L/h) Geo mean (%CV)	$t_{1/2}$ (h) Geo mean (%CV)
150 mg QD	CCI					
200 mg QD						
250 mg QD						
300 mg QD						

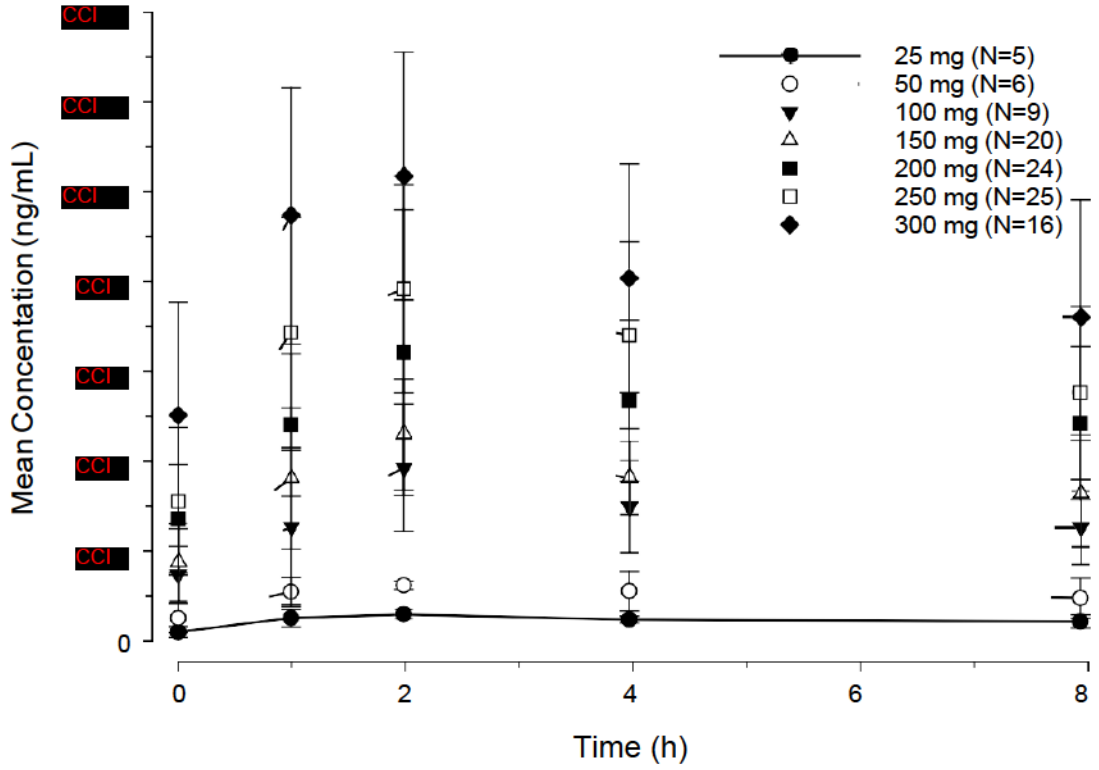
Abbreviations: AUC_{0-24} = area under the concentration-time curve from time 0 to 24 hours; CL/F = apparent oral clearance; C_{max} = maximum drug concentration, Geo mean = geometrical mean, N = number of subjects; PK = pharmacokinetic; QD = once daily; %CV = coefficient of variation in percent; $t_{1/2}$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

[a] N= 5; [b] N= 8; [c] N= 18; [d] N= 16; [e] N= 20; [f] N= 16; [g] N= 15

Data cutoff date: March 30, 2020.

CCI





Data cutoff date: March 30, 2020

Single doses of 200 mg LOXO-305 were investigated in a study in healthy volunteers (LOXO-BTK-20014, Pilot Food Effect study) in which the PK was determined. Following a single dose of 200 mg LOXO-305 to patients or healthy subjects, AUC from 0 to 8 hours was similar between the two groups and C_{max} was approximately CCI% higher in healthy subjects, as shown in the table below (data on file at the time of protocol development).

Table 2 Pharmacokinetic of LOXO-305 Following a Single 200-mg Dose of LOXO-305 in Cancer Patients (Study LOXO-BTK-18001, Cycle 1 Day 1) and Healthy Subjects (Study LOXO-BTK-20014)

Parameter	Healthy Volunteers[a]			Cancer Patients[b]		
	Geometric Mean	CV	n	Geometric Mean	CV	n
CCI						

Abbreviations: AUC_{0-8} =area under the concentration-time curve from 0 to 8 hours; CV=coefficient of variation; C_{max}=maximum concentration; n = number of subjects.
a LOXO-BTX-20014, 200 mg single dose, fasted
b LOXO-BTK-18001, 200 mg single dose, fasted

In healthy volunteers, the geometric mean single-dose C_{max} of approximately CCI ng/mL following a 200-mg single dose is CCI below the NOEL (in rat, C_{max} CCI ng/mL) for micronuclei induction.

1.4. Study Rationale

When developing new drugs for clinical indications, it is necessary to collect data on the safety, tolerability, and PK in order to support further development of the compound as a useful clinical candidate and determine dose levels and dose intervals for subsequent studies. This study will assess the safety, tolerability, and PK of LOXO-305 in healthy subjects at higher dose levels than previously administered in this population to determine the single dose of LOXO-305 needed to reach therapeutic and supratherapeutic exposures of LOXO-305 to design a potential clinical study to determine the effect of LOXO-305 in the QT interval.

1.5. 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.

Doses of LOXO-305 up to 300 mg QD are currently being investigated in the ongoing global Phase 1/2 study in cancer patients, LOXO-BTK-18001. Single doses of 200 mg LOXO-305 were investigated in a study conducted in healthy volunteers (LOXO-BTK-20014). LOXO-BTK-20014 is a pilot food effect study evaluating the effects of food and of a proton-pump inhibitor (omeprazole) on the PK of LOXO-305. Single doses of 200 mg LOXO-305 are currently being investigated in a study conducted in healthy volunteers (LOXO-BTK-20006). LOXO-BTK-20006 is a drug-drug interaction study evaluating the effects of a strong CYP3A4 inhibitor (itraconazole) and a strong CYP3A4 inducer (rifampin) on the PK of LOXO-305.

From AE data reported following LOXO-305 administration in 10 healthy volunteers in the LOXO-BTK-20014 study, all TEAEs (headache, nausea, and vomiting) were Grade 1 in severity and considered related to LOXO-305. All 3 events occurred were reported by 1 subject and resolved by EOT (data on file at the time of protocol development). There were no AEs reported following LOXO-305 administration in 3 healthy volunteers in the LOXO-BTK-20006 study from preliminary data available (data on file at the time of protocol development).

The doses of LOXO-305 administered in this study are not anticipated to induce any potential risk to subjects participating in this study.

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-escalation procedures and safety monitoring practices employed by this protocol (ie, reviewing AE reporting, conducting physical examinations and clinical laboratory evaluations, measuring vital signs, and performing 12-lead ECGs) 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 safety and tolerability of single oral doses of LOXO-305 when administered to healthy adult subjects.

2.1.2. Secondary Objective

The secondary objective of the study is:

- To assess the PK of single oral doses of LOXO-305 when administered to healthy adult subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

Safety

The primary endpoint of this study is to assess the safety and tolerability of LOXO-305 at single doses ≥ 300 mg. This study will investigate the safety and tolerability of single doses (ie, potential therapeutic and supratherapeutic exposures) of LOXO-305 when administered to healthy subjects. Ascending doses up to and possibly including 900 mg will be investigated.

Safety and tolerability will be assessed by monitoring AEs and concomitant medications, performing physical examinations and clinical laboratory evaluations, measuring vital signs, and performing 12-lead ECGs. These safety and tolerability endpoints are deemed adequate to detect any safety signals when the planned dose range of LOXO-305 is administered to healthy subjects.

2.2.2. Secondary Endpoints

Pharmacokinetic

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

- area under the concentration-time curve from hour 0 to 24 hours postdose (AUC_{0-24})
- area under the concentration-time curve from hour 0 to the last measurable concentration (AUC_{0-t})
- area under the concentration-time curve from time 0 extrapolated to infinity (AUC_{0-inf})
- percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$)

- C_{max}
- time to maximum observed plasma concentration (t_{max})
- apparent terminal elimination rate constant (λ_z)
- apparent systemic clearance (CL/F)
- apparent volume of distribution at terminal phase (V_z/F)
- apparent plasma terminal elimination half-life ($t_{½}$).

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an open-label, single-ascending dose study to evaluate the safety, tolerability, and PK of LOXO-305.

Up to 4 cohorts are planned for evaluation. In each cohort, 6 healthy adult subjects are planned for evaluation. Subjects will participate in only 1 cohort. In each cohort, subjects will receive a single oral dose of LOXO-305 on Day 1. Each cohort will include a sentinel group of 2 subjects will be dosed at least 48 hours before the remaining 4 subjects (following review of all available safety data).

A single oral dose of LOXO-305 will be administered on Day 1 for each cohort as follows:

- Cohort 1 (Treatment A): 300 mg
- Cohort 2 (Treatment B): up to 600 mg
- Cohort 3 (Treatment C): up to 900 mg.

One additional cohort (6 subjects) may be enrolled if it is deemed appropriate to repeat any dose level, or to add an interim dose level or levels (equal to or lower than 900 mg), as determined by the Sponsor in consultation with the Investigator (or designee), depending on the safety, tolerability, and PK results from the prior cohort(s). Dosing will not exceed 900 mg in any subject, nor will any subject be given a dose for which the C_{max} would exceed CCI ng/mL.

Dose escalation to a higher dose level (ie, next cohort) will not take place until the Investigator (or designee) and the Sponsor have reviewed all pertinent safety/tolerability data (ie, physical examinations, ECGs, vital sign measurements, clinical laboratory evaluations, and adverse events [AEs]) through a minimum of 168 hours (Day 8) and have determined that adequate safety and tolerability from the previous, lower dose, cohort has been demonstrated to permit proceeding to the next cohort. Pharmacokinetic data through at least 72 hours (approximately 3 half-lives) after dosing will be reviewed to guide the dose-escalation decision. Data from a minimum of 4 subjects will be reviewed in order to make a dose escalation decision. Dose-escalation criteria and stopping rules are described in Section 5.5.

Each treatment (A, B, and C) will be administered orally in the morning following a fast of at least 10 hours prior to and 4 hours after dosing.

The PK sampling will be obtained for 168 hours after administration of each dose of LOXO-305.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days 29 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Subjects will be confined at the CRU from the time of Check-in (Day -1) until EOT on Day 8 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. A follow up phone call will occur for all subjects who received 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 46 days (Screening through follow-up phone call).

Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

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

In this study, physical examinations, 12-lead ECGs, vital 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 AEs (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.

3.2. Discussion of Study Design

When developing new drugs for clinical indications, it is necessary to collect data on the safety, tolerability, and PK to support further development of the compound as a useful clinical candidate and determine dose levels and dose intervals for subsequent studies. This study will assess the safety, tolerability, and PK of LOXO-305 in healthy subjects at higher dose levels than previously administrated in this population so as to determine the single dose of LOXO-305 needed to reach therapeutic and supratherapeutic exposures of LOXO-305 to design a potential clinical study to determine the effect of LOXO-305 on the QT interval.

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

The three planned single doses of 300 mg, 600 mg, and 900 mg in this study are designed to yield a C_{max} of LOXO-305 up to CCI higher than the therapeutic C_{max} (CCI ng/mL, Table 1) at the recommended Phase 2 dose of 200 mg QD that may arise from intrinsic or

extrinsic factors that lead to higher exposures in cancer patients. A fourth optional dose level, not to exceed 900 mg, may be used if necessary, to further define the dose-exposure relationship.

The starting single dose of 300 mg in this study is expected to produce a C_{max} that is approximately CCI ng/mL (CCI therapeutic). As LOXO-305 shows generally linear PK in cancer patients (Table 1), if exposure also increases linearly with dose in healthy subjects, the proposed single doses of 600 mg and 900 mg would produce C_{max} values of CCI and CCI, respectively. As the PK linearity of doses greater than 300 mg is not known, the PK of LOXO-305 following each dose will be evaluated prior to administering higher doses, and no dose will be given for which the geometric mean C_{max} is predicted to exceed CCI based on the PK observed at lower doses.

4. SELECTION OF STUDY POPULATION

4.1. Screening Procedures

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

1. Inclusion/exclusion criteria
2. Informed consent
3. Demographic data
4. Medical history (including review of medication[s])
5. Height, weight, and body mass index (BMI)
6. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
7. Vital sign measurements (including oxygen saturation, oral temperature, respiratory rate, and supine blood pressure [BP] and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
8. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
9. Clinical laboratory evaluations (Section 7.2.2; 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) core antibody, human immunodeficiency virus (HIV) antibody, and SARS-CoV-2 (COVID-19) via polymerase chain reaction testing ([PCR] or equivalent (Appendix 2)
11. Hemoglobin A1c (HbA1c) test (Appendix 2)
12. Screen for selected drugs of abuse, including cotinine and alcohol (Appendix 2)
13. Estimated glomerular filtration rate (Appendix 2)
14. Serum pregnancy test (for female subjects only; Appendix 2)

15. Follicle-stimulating hormone (FSH) test (for post-menopausal female subjects only; Appendix 2)
16. Thyroid-stimulating hormone (TSH) test (Appendix 2)

4.2. Check-in Procedures (Day -1)

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

1. Review of inclusion/exclusion criteria
2. Interim medical history, including concomitant medication(s)
3. Weight and BMI
4. Complete physical examination (Section 7.2.5)
5. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
6. Vital sign measurements (including oxygen saturation, oral temperature, respiratory rate, and supine BP and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
7. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
8. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
9. Screen for COVID-19 via PCR or equivalent
10. Screen for selected drugs of abuse, including cotinine and alcohol (Appendix 2)
11. Estimated glomerular filtration rate (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 enrollment. Prior to dosing, the Sponsor will provide approval of subjects selected for enrollment by the Investigator (or designee).

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

4.3. Inclusion Criteria

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

1. Males, and females of non-childbearing potential, between 18 and 55 years of age, inclusive, at Screening.
2. Within BMI range 18.0 to 32.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital 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 study drug administration) or post-menopausal (defined as at least 12 months post-cessation of menses without an alternative medical cause). Post-menopausal status will be confirmed with a screening serum FSH level ≥ 40 mIU/mL. All female subjects must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin; serum quantitative human chorionic gonadotropin tests may be used for confirmation as needed) at Screening and Check-in (Day -1). Female subjects are required to refrain from donation of ova from Check-in (Day -1) until 6 months after administration of study drug.
5. Male subjects who are capable of fathering a child must agree to use 1 of the following methods of contraception from the time of the dose administration through 6 months after the last dose of LOXO-305 administration:
    a. Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1). If documentation is not available, male subjects must follow 1 of the contraception methods below:
        i. Male condom with spermicide, or
        ii. A male subject must ensure that their female partner meets 1 of the following criteria:
            1. intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
            2. established use of oral, implanted, 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 male partner's study drug administration); or
            4. be post-menopausal with amenorrhea for at least 1 year prior to dosing 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 through 6 months after study drug administration, he must agree to use contraception as described above.

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

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

6. Able to swallow multiple capsules.
7. Able to understand and provide written informed consent.
8. Able to comply with all study procedures, including the 8-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 the first dose administration (Day 1)
        ii. Symptomatic angina pectoris within 6 months prior to the first dose administration (Day 1)
        iii. New York Heart Association Class ≥ 2 congestive heart failure within 6 months prior to the first dose administration (Day 1)
        iv. Congenital prolonged QT syndrome
        v. Ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        vi. Arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention
        vii. Ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)

viii. Significant screening ECG abnormalities:

1. left bundle branch block
2. second degree atrioventricular (AV) block, type 2, or third-degree AV block
3. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec
4. ECG findings deemed abnormal with clinical significance by the Investigator (or designee) at Screening, Check-in (Day -1), or prior to dosing on Day 1.

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, including:

   a. oral 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)

   For these parameters, out-of-range values that are not clinically significant (as determined by the Investigator [or designee]) may be repeated twice during Screening, Check-in (Day -1), and predose on Day 1. Note: Rechecks of pulse rate and BP values will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked pulse rate and/or BP values if the values fall within the ranges stated above.

3. Abnormal laboratory values (hematology panel, UA, clinical chemistry panel [fasted at least 8 hours], excluding those further defined in exclusion criteria #5, #6, #7, and #8 below) determined to be clinically significant by the Investigator (or designee), and Sponsor at Screening and/or Check-in (Day -1) as confirmed by repeat assessment.
4. Clinically significant abnormality, as determined by the Investigator (or designee), from physical examination at Check-in (Day -1).
5. Abnormal liver function tests (LFTs), as defined by aspartate aminotransferase, alanine aminotransferase, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or Check-in (Day -1). Rechecks of LFTs, amylase, and lipase will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges.
6. Any clinically significant deviations from normal ranges in creatine kinase (CK) unless approved by the Investigator (or designee) and Sponsor. Rechecks of CK will be permitted up to 2 times to confirm eligibility for study participation if the out-of-range values are stable or trending down and the Investigator (or designee) and the Sponsor deem that the results are not clinically significant and will not impact study conduct.

7. Estimated glomerular filtration rate ≤ 90 mL/minute/1.73m^2 at Screening or Check-in (Day -1) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.
8. Hemoglobin, white blood cell count, and platelet counts below the lower limit of normal range at Screening or Check-in (Day -1). Rechecks of hemoglobin, white blood cell count, and platelet counts will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges.
9. Positive serologic test for HBsAg, HBV core antibody, HCV, or HIV antibody at Screening. Subjects who are positive for HCV by antibody will require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HCV PCR positive or for whom a PCR is unable to be obtained will not be eligible.
10. Positive PCR test (or equivalent) for COVID-19 at Screening or Check-in (Day -1). Further details regarding COVID-19 testing (including procedures who test positive at any time throughout CRU confinement) are specified in separate documents.
11. Subjects with known ongoing alcohol and/or drug abuse within 2 years prior to Screening, or evidence of such abuse as indicated by the laboratory assays 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).
12. 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.
13. Consumption of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
14. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET.
15. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
16. Participation in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to the first dose administration (Day 1).
17. Use or intention to use any prescription or over-the-counter medications (including, but not limited to, any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers (including herbal products such as St. John's wort), strong P-glycoprotein (P-gp) inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, herbal products, natural or herbal supplements, and hormone-replacement therapy [HRT]) within 14 days prior to the first dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
18. History of a major surgical procedure within 30 days prior to Screening.
19. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator (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.

20. Poor peripheral venous access.
21. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
22. Receipt of blood products within 2 months prior to Check-in (Day -1).
23. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET.
24. Significant history or clinical manifestation of any allergic, dermatological, biliary, hepatic, gastrointestinal, renal, metabolic, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac 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.
25. History of diabetes mellitus; HbA1c $\geq$ 6.5%.
26. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).
27. Have previously completed or withdrawn from any other study investigating LOXO-305 and have previously received the investigational product.
28. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator (or designee), and as confirmed by the Sponsor, within the 30 days prior to the first dosing and through EOT or ET.
29. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

4.5. Subject Number and Identification

Subject numbers will consist of 6 digits in which the first set of 3 digits will identify the site and the second set of 3 digits will identify the subject (eg, 001-101). If subjects are withdrawn by the Investigator (or designee) or voluntarily withdraw prematurely from the study, replacement subjects 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 50 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-151 replaces Subject Number 001-101).

4.6. Removal of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator (or designee) may remove a subject from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn because of the following:

- change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety
- occurrence of AEs

- occurrence of pregnancy
- intake of non-permitted concomitant medication that might affect subject safety or study assessments/objectives, etc.

Notification of withdrawal will immediately be made to the Sponsor. In case of withdrawal, efforts will be made to perform all final study day assessments (Appendix 4). The date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's electronic Case Report Form (eCRF). All withdrawn subjects with AEs that are assessed as related to study drug and which are ongoing at ET may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator (or designee) and confirmed by the Sponsor.

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

- 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 the LOXO-305.

Table 3 Study Drugs

Study Drug	LOXO-305
Form[a]	Tablet
Strength	25 mg
Supplier	Loxo Oncology, Inc.
Manufacturer	Bend Research, Inc.

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

The tablets containing 25 mg LOXO-305 will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificate of Analysis. It will be provided in high-density polyethylene bottles and stored according to the instructions on the label.

Size 0 light blue opaque capsules to over-encapsulate LOXO-305 tablets will be supplied by Covance. LOXO-305 tablets will be over-encapsulated (with 4 tablets of LOXO-305 being placed in each capsule) according to Covance CRUs Standard Operating Procedures (SOPs) and relevant processes.

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 drug 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

Cohort 1 (Treatment A):

- A single oral dose of 300 mg LOXO-305 (12 × 25-mg tablets, over-encapsulated [3 capsules]) following a fast of at least 10 hours prior to and 4 hours after dosing.

Cohort 2 (Treatment B):

- A single oral dose of up to 600 mg LOXO-305 (24 × 25-mg tablets, over-encapsulated [6 capsules], or less depending on the dose chosen) following a fast of at least 10 hours prior to and 4 hours after dosing.

Cohort 3 (Treatment C):

- A single oral dose of up to 900 mg LOXO-305 (36 × 25-mg tablets, over-encapsulated [9 capsules], or less depending on the dose chosen) following a fast of at least 10 hours prior to and 4 hours after dosing.

One additional cohort (6 subjects) may be enrolled if it is deemed appropriate to repeat any dose level, or to add an interim dose level or levels (equal to or lower than 900 mg), as determined by the Sponsor in consultation with the Investigator (or designee), depending on the safety, tolerability, and PK results from the prior cohort(s). Dosing will not exceed 900 mg in any subject, nor will any subject be given a dose for which the C_{max} would exceed CCI ng/mL.

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

Each unit dose will be prepared by qualified CRU staff. Each unit dose container will be appropriately labelled.

Appropriate unit dose(s), as described above, will be administered to subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at a specific time, the exact dose time of subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual dose time will be recorded in the source documents and transcribed into the eCRF.

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

Subjects will not lay supine for 4 hours following LOXO-305 dose administration, except as necessitated by the occurrence of an AE(s) and/or study procedure(s).

5.3. Randomization

This is a nonrandomized study.

5.4. Blinding

This is an open-label study.

5.5. Dose Escalation Criteria and Stopping Rules

Dose escalation to the next dose level (ie, next cohort) will not take place until the Investigator (or designee) and the Sponsor have determined that adequate safety and tolerability data (ie, physical examinations, ECGs, vital sign measurements, clinical laboratory evaluations, and AEs through 168 hours [Day 8] following dosing on Day 1) from the previous, lower dose, cohort has been demonstrated to permit proceeding to the next cohort. A sufficient period of time will be allowed between dosing (168 hours [Day 8], following dosing on Day 1) of the prior cohort and the dosing of the next cohort in order for the Investigator (or Designee) and the Sponsor to adequately review the safety and tolerability data from the prior cohort. Pharmacokinetic data through at least 72 hours (approximately 3 half-lives) will be reviewed to guide dose-escalation decisions or for selection of an alternate dose for evaluation, and/or to confirm the sampling schedule. Data from a minimum of 4 subjects will be reviewed in order to make a dose escalation decision.

The Investigator (or designee) and the Sponsor will make 1 of the following determinations:

1. To continue with the study as planned.

2. To continue with the study and add additional safety evaluations to subsequent cohorts.
3. In the event of the following occurrence:
    a. One subject at a given dose level experiences a drug-related Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 toxicity (which is not an SAE), which is deemed clinically significant by the Investigator (or designee), with agreement from the Sponsor, a decision will be made as follows:
        - Adjust to an intermediate dose between the current dose and the next planned dose;
        - Adjust to an intermediate dose between the current dose and the previous lower dose;
        - Dose administration may be permitted to continue as deemed by the Investigator (or designee), with agreement from the Sponsor, where the safety parameter assessed does not pose a subject safety risk based on safety knowledge from prior LOXO-305 studies.
    b. Two or more subjects in a dose level experience a drug-related CTCAE grade ≥ 3 toxicity (which is not an SAE), which are deemed clinically significant by the Investigator (or designee), with agreement from the Sponsor, a decision will be made as follows:
        - Dose administration may be permitted to continue as planned if deemed acceptable by the Investigator (or designee), with agreement from the Sponsor, where the safety parameter assessed does not pose a subject safety risk based on safety knowledge from prior LOXO-305 studies;
        - Evaluate an alternative dose level;
        - The study may be terminated with no additional dose administration to any subjects.
    c. One or more subject(s) in a dose level has a C_{max} of > CCI ng/mL or a predicted C_{max} of ≥ CCI ng/mL in a subsequent dose level, a decision will be made as follows:
        - Adjust to an intermediate dose between the current dose and the previous lower dose;
        - The study may be terminated with no additional dose administration to any subjects.

5.6. 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 will be performed, as appropriate.

5.7. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies (including LOXO-305 tablets and capsules to over-encapsulate LOXO-305) received or procured by Covance. 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 supplies (including all IMP) will be disposed of by the CRU, per the Sponsor's written instructions and/or in accordance with local/state/federal guidelines governing waste disposal of investigational drugs and the CRUs 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 dose administration (Day 1).

All prescription/nonprescription medications and over-the-counter medications (including HRT, herbal products, natural or herbal supplements, except for paracetamol/acetaminophen as referenced above) are prohibited for 14 days prior to dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor. This includes, but is not limited to: moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers (including herbal products such as St. John's wort), strong P-gp inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval.

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

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

6.2. Diet, Fluid, and Activity Control

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

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

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

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

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

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

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of LOXO-305 plasma levels will be collected at the timepoints specified in Appendix 4. The exact time of the study drug administration and the actual time of blood sampling for PK analysis will be recorded on the eCRF.

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

7.1.2. Analytical Methodology

Concentrations of LOXO-305 in plasma will be determined using a validated bioanalytical method. Specifics of the bioanalytical methods will be provided in a separate document.

7.2. Safety and Tolerability Assessments

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

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

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

7.2.1. Adverse Events

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

Subjects will be asked a non-leading HDYF? question such as “Have there been any changes in your health status since Screening/since you were last asked?” at the timepoints specified in Appendix 4 (ie, at Screening [after the ICF is signed], at Check-in [Day -1], at each postdose vital 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 expected adverse reactions.

7.2.2. Clinical Laboratory Evaluations

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

Screens for HCV antibody, HBV core antibody, HBsAg, 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 who test positive at any time throughout CRU confinement) are specified in separate documents.

A urine drug screen for selected drugs of abuse (including cotinine and alcohol) 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.

7.2.3. Vital Signs

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

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

When vital sign measurements are scheduled at the same time as blood draws, the 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 blood draw.

7.2.4. 12-lead Electrocardiogram

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

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

7.2.5. Physical Examination

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

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

This study is planned to enroll up to 24 healthy adult male and female subjects (women of non-childbearing potential only). Six subjects will participate in each cohort.

Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Every attempt will be made to enroll at least 1 subject of each sex in each cohort.

No formal statistical assessment of sample size has been conducted. The sample size chosen for this study is common in single-ascending dose studies and is considered sufficient to achieve the objectives of the study.

8.2. Analysis Populations

8.2.1. Study Populations

The **PK population** will consist of all subjects who received at least 1 dose of LOXO-305, have at least 1 quantifiable PK concentration, and for whom at least 1 PK parameter can be computed. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times the median t_{max}. The impact of protocol deviations on the PK population will be evaluated case-by-case basis.

The **safety population** will consist of all subjects who received 1 dose of LOXO-305. Subjects will be classified into groups based on actual treatment received.

8.3. Pharmacokinetic Analysis

Serial PK blood samples for the analysis of plasma concentrations of LOXO-305 will be collected from predose through 168 hours post-LOXO-305 dose for Treatments A, B, and C.

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

AUC_{0-24}	area under the concentration-time curve from hour 0 to 24 hours postdose, as calculated by the linear trapezoidal method
AUC_{0-t}	area under the concentration-time curve (AUC) from hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
AUC_{0-inf}	AUC from time 0 extrapolated to infinity, calculated using the formula: $AUC_{0-inf} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage extrapolation for AUC_{0-inf}
C_{max}	maximum observed plasma concentration
t_{max}	time to maximum observed plasma concentration

λ_z	apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
CL/F	apparent systemic clearance
$t_{½}$	apparent plasma terminal elimination half-life (whenever possible), where $t_{½} = \ln(2)/\lambda_z$
V_z/F	apparent volume of distribution at terminal phase

Pharmacokinetic calculations will be performed using commercial software such as Phoenix™ WinNonlin® Version 8.1 or higher (Certara USA Inc.).

The λ_z and $t_{½}$ will be calculated by linear least squares regression analysis using the maximum number of points in the terminal log linear phase (eg, 3 or more non-zero plasma concentrations). Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

Pharmacokinetic analysis will use actual times as recorded on the eCRF. All statistical analysis will be performed using SAS® Version 9.4 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

Pharmacokinetic dose proportionality will be assessed for Cohorts 1, 2, and 3. Natural log-transformed $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of LOXO-305 will be evaluated using a power model of the form:

$$ln(parameter) = intercept + slope \times ln(dose) + random\ error$$

For each PK parameter separately, a pooled estimate (across all doses) of slope, corresponding 95% confidence interval, and between-subject CV% will be calculated.

8.4. Safety Analysis

All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory evaluations, physical examination results, concomitant medications, and 12-lead ECGs, will be tabulated and summarized where possible, using descriptive methodology, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of LOXO-305. 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 WHO Drug Dictionary (WHO Drug Global B3, September 2019) and AEs will be coded using 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 clinician.

The Data Management Plan will be approved by the Sponsor.

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

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

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

8.6. Quality Control and Quality Assurance

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

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

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

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

9.2. Site Initiation Visit/Investigator Meeting

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

9.3. Disclosure

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

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

9.4. Monitoring

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

9.5. Institutional Review Board

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

IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator (or designee).

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

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

9.6. Informed Consent

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

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

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

9.7. Records

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

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

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

9.8. Reference to Declaration of Helsinki/Basic Principles

The study procedures outlined in this protocol will be conducted in accordance with the US CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), Applications for FDA Approval to Market a New Drug (21 CFR 314), and Radioactive Drugs for Certain Research Uses (21 CFR 361.1), as appropriate. As such, these

sections of US Title 21 CFR, along with the applicable 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 3.1). 2020.

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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 relevant adverse changes in laboratory parameters observed in a subject during a clinical study.

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

Categorization of Adverse Events

The severity of AEs will be categorized based on the National Cancer Institute 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 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 an 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 immediately if they discover their sexual partner is pregnant. In this instance, the partner must provide written consent before pregnancy information can be collected. When a CRU becomes aware that the female partner of a male subject is pregnant, they are to contact the Investigator (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 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 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 or if it is not listed at the specificity or severity that has been observed for an unapproved investigational medicinal product.

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. Final determination of whether an event represents a suspected unexpected serious adverse reaction 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] SARS-CoV-2 (COVID-19) Testing
		Coagulation Parameters:
		Partial thromboplastin time Prothrombin time International normalized ratio
		Serology:[b]
		Human immunodeficiency virus (HIV) antibody Hepatitis B surface antigen (HBsAg) Hepatitis B virus (HBV) core antibody Hepatitis C virus (HCV) antibody
		For Female Subjects only:
	Urinalysis:	Pregnancy test (serum qualitative, serum quantitative may be used for confirmation if needed)[c] Follicle-stimulating hormone (post-menopausal female subjects only)[b]
Urine Drug Screen:[a]	Bilirubin Color and appearance Glucose Ketones Leukocyte esterase Nitrite Occult blood pH and specific gravity Protein Urobilinogen Microscopic examination including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)	
Including, but not limited to, the following: Alcohol (ethanol) 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 End of Treatment (EOT) or Early Termination (ET) only.

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
LOXO-305 pharmacokinetic sampling	4.0	20	80.0
Clinical laboratory evaluations: Hematology Clinical chemistry Coagulation parameters	 4.0 4.0 3.0	4	44.0
Serum pregnancy test (female subjects only)	4.0	3	12.0
Serum follicle-stimulating hormone (FSH; post-menopausal female subjects only) and thyroid-stimulating hormone (TSH)	4.0	1	4.0
		Total:	**152.0 mL**

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 200 mL.

Appendix 4: Schedule of Assessments

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Study Conduct							Clinic Discharge/ EOT/ET[t]	Follow-up Phone Call (EOS)
			1	2	3	4	5	6	7	8	7 (± 2) days post EOT/ ET[v]
Confined to the CRU		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[c]	X[c]									
Physical Examination[d]		X								X	
12-lead ECG[e]	X	X	X	X		X				X	
Vital Signs[f]	X[g,h]	X[g,h]	X[h]	X	X	X	X	X	X	X[g,h]	
HDYF? Inquiry[i]	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
LOXO-305 Administration			X[k]								
CCI											
Clinical Laboratory Evaluations[n]	X	X				X			X[u]	X[u]	
Estimated Glomerular Filtration Rate	X	X									
Hepatitis and HIV Screen	X										
COVID-19 Testing[o]	X	X									
HbA1c Test	X										
Drug Screen[p]	X	X									
Prior and Concomitant Medications[q]	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[r]	X	X							X[u]	X[u]	
FSH Test[s]	X										
TSH Test	X										

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; COVID-19 = SARs Coronavirus 19; CRU = Clinical Research Unit; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; ICF = Informed Consent Form; PK = pharmacokinetic; SAE = serious adverse event; TSH = thyroid-stimulating hormone; UA = urinalysis.

a. For details on study procedures, see Section 7.
b. Interim medical history only.
c. Height collected at Screening only, body mass index based on Screening height.
d. A complete physical examination will be performed at Check-in (Day -1). An abbreviated physical examination will be performed on Day 8 (End of Treatment [EOT]) or Early Termination (ET).
e. 12-lead electrocardiograms (ECGs) will be obtained prior to and as close as possible to the scheduled blood draws at Screening and Check-in (Day -1), and at the following times related to administration of each Treatment: Day 1 (predose and 2 and 4 hours after LOXO-305 dosing), Day 2, Day 4, and Day 8 (EOT) or ET. 12-lead ECGs will be collected after the subject has rested in the supine position for at least 10 minutes.

f. Vital sign measurements (supine blood pressure [BP] and pulse rate) will be obtained at Screening and Check-in (Day -1), at the following times related to administration of each Treatment: predose (within 45 minutes prior to dosing), 45 minutes postdose, and 2, 4, 24, 48, 72, 96, 120, 144, and 168 hours postdose (Day 8 [EOT]) or ET. Vital sign measurements should be carried out prior to and as close as possible to the scheduled blood draw. BP and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.
g. Oral temperature and respiratory rate will be obtained at Screening and Check-in (Day -1) and on Day 8 (EOT) or ET.
h. Oxygen saturation will be measured via pulse oximetry once at Screening, Check-in (Day -1), predose on Day 1, and Day 8 (EOT) or ET.
i. A How Do You Feel? 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 (AEs) and serious AEs (SAEs) will be collected beginning at informed consent. Adverse events will be recorded throughout the study (ie, from signing of the Informed Consent Form [ICF] until End of Study [EOS], or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed 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. Subjects will be assigned to 1 cohort only, Cohort 1 (Treatment A/300 mg LOXO-305), Cohort 2 (Treatment B/600 mg LOXO-305), or Cohort 3 (Treatment C/900 mg LOXO-305)

CCI

n. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and urinalysis (UA) will be performed.
o. 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.
p. Drugs of abuse urine test, including cotinine and alcohol. Results from the drugs of abuse tests will be used to determine subject eligibility per the inclusion/exclusion criteria.
q. Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 14 days prior to study drug administration (Day 1) for prescription medications and non-prescription medication, will be recorded on the subject's electronic Case Report Form.
r. Female subjects only.
s. Post-menopausal female subjects only.
t. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 8. ET 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 at the EOT visit. Clinical laboratory evaluations for clinical chemistry, hematology, coagulation, and UA and 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.
u. Clinical laboratory evaluations and pregnancy test (female subjects only) will be performed on the day prior to subject release from the CRU (Day 7) if the subject completes the study (EOT). Clinical laboratory evaluations and pregnancy test (female subjects only) will be performed on the day of subject release from the CRU if the subject terminates early (ET).
v. To be conducted 7 days (± 2 days) following EOT or ET. EOS is defined as when the subject attends 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 (including subjects who are terminated early) will receive a follow-up phone call.