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An Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Phalmacokinetic Study of LOXO-305 Administered to Fasted Renally Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

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Study Site:
Multiple Sites

Sponsor Signatory:
PPD

Principal Investigator:
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SPONSOR APPROVAL

I have read the protocol and approve it:

18-Feb-21 | 12:51:42 PST

Date

PPD Consulting to
Loxo Oncology, Inc.

INVESTIGATOR AGREEMENT

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

Name, Qualifications Principal Investigator	Date

STUDY IDENTIFICATION

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SYNOPSIS

Study Title

An Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-305 Administered to Fasted Renally Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Objectives

The primary objective of the study is to evaluate the pharmacokinetic (PK) profile of LOXO-305 in subjects with impaired renal function compared to matched-control healthy subjects.

The secondary objective of the study is to evaluate safety and tolerability of LOXO-305 in subjects with impaired renal function and matched-control healthy subjects.

Study Design

This study is an open-label, nonrandomized, multi-center, single-dose, parallel-group study to determine the PK, safety, and tolerability of LOXO-305 administered orally at a dose of 200 mg to fasted adult males and females with impaired renal function and healthy subjects with normal renal function. Renal function will be classified based on the baseline estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation. **Baseline eGFR will be obtained for all subjects (ie, subjects with renal impairment and matched-control healthy subjects) by taking the mean of the eGFR obtained from Screening and from historical values obtained within a 3-month period from Screening. If no historical eGFR value is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the 2 values will be used as the baseline eGFR for group assignment.** Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each group (ie, matched-control healthy subjects and subjects with severe renal impairment [and subjects with mild and/or moderate renal impairment, if they are enrolled]) to categorize subjects' renal impairment status. The eGFR based on CKD-EPI equation will be repeated at Check-in (Day -1) to confirm renal impairment status. For matched-control healthy subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the eGFR (based on the CKD-EPI equation), at the Investigator's (or designee's) discretion.

Subjects with severe renal impairment (Group 4), and matched-control healthy subjects with normal renal function (Group 1) will begin enrolling in the study first. Subjects will be recruited so that up to 8 subjects with severe renal impairment and up to 8 subjects with normal renal function are enrolled, with the goal of having at least 6 subjects with severe renal impairment and at least 6 matched-control healthy subjects complete the study.

Subjects will be enrolled within the following groups based on their eGFR values calculated using the CKD-EPI equation at Screening and repeated at Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 1: Matched-control healthy subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2)
- Group 4: Subjects with severe renal impairment (eGFR: < 30 mL/min/1.73 m^2)

Continuous review of the safety data and PK data (if available) from up to 8 subjects with severe renal impairment and up to 8 matched-control healthy subjects with normal renal function will be conducted after these subjects have completed all study-related assessments through 72 hours (approximately 3 half-lives) postdose, at a minimum. The safety data will include adverse events (AEs) and serious AEs (SAEs), vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory evaluations.

Following continuous review of the safety data and PK data from up to 8 subjects with severe renal impairment (Group 4) and up to 8 matched-control healthy subjects with normal renal function (Group 1), subjects with mild renal impairment (Group 2) and/or moderate renal impairment in (Group 3) may be enrolled if deemed necessary by the Sponsor. If no clinically relevant effect on PK is observed in subjects in Group 1 and Group 4, enrollment of subjects in Group 2 and/or Group 3 will not occur.

If the Sponsor deems it necessary to enroll subjects with mild and/or moderate renal impairment, subjects will be recruited so that up to 8 subjects with mild renal impairment, up to 8 subjects with moderate renal impairment, and up to an additional 16 matched-control healthy subjects with normal renal function may be enrolled, with the goal of having at least 6 subjects with mild renal impairment and at least 6 subjects with moderate renal impairment and their matched-control healthy subjects complete the study. Enrollment and dosing for subjects in Group 2 and/or Group 3 may only occur after the safety and PK data for subject(s) in Group 1 and Group 4 through a minimum of 72 hours postdose are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Subjects will be enrolled within the following groups based on their eGFR values calculated using the CKD-EPI equation at Screening and repeated at Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 2: Subjects with mild renal impairment (60 ≤ eGFR < 90 mL/min/1.73 m^2)
- Group 3: Subjects with moderate renal impairment (30 ≤ eGFR < 60 mL/min/1.73 m^2)

Baseline eGFR will be obtained for all subjects (ie, subjects with renal impairment and matched-control healthy subjects) by taking the mean of the eGFR obtained from Screening and from historical values obtained within a 3-month period from Screening. If no historical eGFR value is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the 2 values will be used as the baseline eGFR for group assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each group (ie, matched-control healthy subjects and subjects with severe renal impairment [and subjects with mild and/or moderate renal impairment, if they are enrolled]) to categorize subjects' renal impairment status. The eGFR based on CKD-EPI equation will be repeated at Check-in (Day -1) to confirm renal impairment status. For matched-control healthy subjects, a single assessment of actual creatinine clearance

computed over a 24-hour urine collection may be used in place of the eGFR (based on the CKD-EPI equation), at the Investigator's (or designee's) discretion.

Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the completed renal impairment subject(s). Should another renal impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different renal impairment group. Each subject with normal renal function may be matched with up to 1 subject within each renal impairment group.

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

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

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. Subjects will be dosed on Day 1. A follow-up phone call will occur for all subjects who received a dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET.

Pharmacokinetic samples will be obtained through 168 hours postdose.

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 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

A total of up to 24 subjects with renal impairment (up to 8 subjects with severe impairment, and, if necessary, up to 8 subjects with moderate impairment, and/or up to 8 subjects with mild impairment, per eGFR using the CKD-EPI equation) and approximately 8 to 24 matched-control healthy subjects with normal renal function will be enrolled in the study with the goal of having at least 6 subjects from each renal impairment group enrolled in the study and at least 6 subjects with normal renal function complete the study.

Main Criteria for Inclusion

Male subjects and female subjects of non-childbearing potential, between 18 and 75 years of age, inclusive, at Screening, and within BMI range 18.5 to 40.0 kg/m^2, inclusive. Subjects will be in good general health, except for additional specific inclusion criteria related to subjects with renal impairment, based on medical history, physical examination findings, vital sign measurements, 12-lead ECG, and 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 (or designee) as 100-mg tablets for oral administration.

On the morning of Day 1, after at least an 8-hour fast, a single oral dose of 200 mg LOXO-305 will be administered with approximately 240 mL of water. No food will be allowed for up to 2 hours postdose. Water will be restricted for 1-hour predose and 1-hour postdose, with the exception of water administered for dose administration. Glucose tablets may be administered as needed for treatment of hypoglycemia in renally impaired subjects with diabetes.

Duration of Subject Participation in the Study:

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

Length of CRU 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 postdose. A sample for assessment of unbound plasma concentrations of LOXO-305 will be collected predose.

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 (AUC) from hour 0 to the last measurable concentration (AUC_{0-t}), AUC from hour 0 extrapolated to infinity (AUC_{0-inf}), percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$),

maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), apparent terminal elimination rate constant (λ_z), apparent systemic clearance (CL/F), apparent plasma terminal elimination half-life ($t_{½}$), mean residence time (MRT), unbound fraction (f_u), and apparent volume of distribution during the terminal phase (V_z/F).

The f_u value determined for each subject will be used to calculate the following unbound LOXO-305 PK parameters for each individual subject: Unbound C_{max} ($C_{max,u}$), unbound AUC_{0-t} ($AUC_{0-t,u}$), unbound AUC_{0-inf} ($AUC_{0-inf,u}$), unbound CL/F ($CL/F_{,u}$), and unbound V_z/F ($V_z/F_{,u}$).

Safety:

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

Statistical Methods

Pharmacokinetics

The primary analysis planned for this study is to evaluate the PK of LOXO-305 after a single dose in subjects with renal impairment compared to subjects with normal renal function.

Paired t-tests will be performed to assess the differences in PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) between each renal impairment group versus the corresponding matched-control healthy group with respect to 1 to 1 matching. The analysis will be based on the natural log (ln)-transformed PK parameters. Geometric mean ratios and their corresponding 90% confidence intervals (CIs) will be calculated using the exponentiation of the mean difference and the CIs obtained for the difference in mean between each renal impairment group and the matched-control healthy group.

In addition, an analysis of covariance (ANCOVA) will be performed on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. The ANCOVA model will contain a categorical factor of population for subjects with varied-degree renal impairment (severe, moderate, and mild) and matched-control healthy subjects, a categorical covariate (sex), and continuous covariates (age and BMI). Ratios of least squares means and 90% CIs will be calculated using the exponentiation of the difference between renal function cohort least squares means from the ANCOVA analyses on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. In addition, an ANCOVA will be performed on the ln-transformed $AUC_{0-t,u}$, $AUC_{0-inf,u}$, and $C_{max,u}$.

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

The relationship between LOXO-305 PK parameters (ie, C_{max} and AUC) and measures of renal function (such as eGFR and creatinine clearance) may be explored using a linear regression approach or other methods, as indicated in the SAP. The effect of covariates such as age, BMI, and sex may be investigated.

Safety

All safety assessments, including AEs, SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and 12-lead ECGs, will be tabulated, and summarized where possible, using descriptive methodology by renal function group and, 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 hour 0 extrapolated to infinity
ADL	Activities of Daily Living
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from hour 0 extrapolated to infinity
$AUC_{0\text{-}inf,u}$	unbound area under the concentration-time curve from hour 0 extrapolated to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from hour 0 to the last measurable concentration
$AUC_{0\text{-}t,u}$	unbound area under the concentration-time curve from hour 0 to the last measurable concentration
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BP	blood pressure
BSEP	bile salt exporter pump
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval(s)
CL/F	apparent systemic clearance
$CL/F_{,u}$	unbound apparent systemic clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
$C_{max,u}$	unbound maximum observed plasma concentration
COVID-19	SARS-CoV-2
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
eGFR	estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ET	Early Termination

FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
f_u	unbound fraction
GLP	Good Laboratory Practice
hERG	human ether-à-go-go-related gene
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDYF?	How Do You Feel?
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
IC_{90}	concentration required for 90% inhibition
ICF	Informed Consent Form
IgM	immunoglobulin M
IRB	Institutional Review Board
IUD	intrauterine device
LFT	liver function test(s)
ln	natural log
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
MRT	mean residence time
NHL	non-Hodgkin lymphoma
NOEL	no observed effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event(s)
SAD	single ascending dose
SAP	Statistical Analysis Plan
SDD	spray-dried dispersion
SLL	small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent plasma terminal elimination half-life

TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time to maximum observed plasma concentration
TSH	thyroid-stimulating hormone
UA	urinalysis
V_z	volume of distribution
V_z/F	apparent volume of distribution
$V_z/F_{,u}$	unbound apparent volume of distribution
WHO	World Health Organization
λ_z	apparent terminal elimination rate constant

1. INTRODUCTION

Refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product , LOXO-305.[1]

1.1. Background

LOXO-305 (also known as LY3527727) is a selective inhibitor of the Bruton's tyrosine kinase (BTK) being developed by Loxo Oncology. LOXO-305 is distinct from the approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) in several important ways including on the basis of its selectivity, favorable absorption, distribution, metabolism, and excretion properties, and non-covalent binding mode.[2] These features enable LOXO-305 to achieve pharmacokinetic (PK) exposures that exceed the BTK concentration resulting in 90% inhibition (IC_{90}) at trough, and thus deliver tonic BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. Moreover, the non-covalent binding mode of LOXO-305 is unaffected by BTK C481 substitutions, a common mechanism of drug resistance described for all available covalent inhibitors.[3,4,5,6,7] Finally, LOXO-305 is also a highly selective molecule that is more than 300-fold more selective for BTK versus 370 other kinases tested with no significant inhibition of non-kinase off-targets at 1 μM, thus limiting the potential for off-target mediated toxicities. Collectively, these unique properties of LOXO-305 are expected to deliver more potent, continuous, and selective inhibition of BTK in a variety of settings, potentially resulting in increased efficacy. Of note, the activity of LOXO-305 in diverse preclinical model systems supports this underlying hypothesis.[2]

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

1.2. Nonclinical Pharmacokinetics and Toxicology Summary

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

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

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

LOXO-305 was metabolized slowly by human microsomal fractions and hepatocytes. The low rates of metabolism in both these human in vitro systems suggest that LOXO-305 will have low clearance in humans. In vitro data with 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% inhibitory concentration (IC_{50}) 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} (CCI ng/mL) at the proposed clinical therapeutic dose of 200 mg QD. Furthermore, there were no LOXO-305-related abnormalities in rhythm or waveform morphology in the GLP 28-day repeated-dose toxicity study in dogs at the low- and mid-dose groups based on comparison of predose and postdose electrocardiogram (ECG) recordings. The high dose (90/60 mg/kg/dose twice daily [BID]) was not evaluated as animals in this group were moribund/debilitated and were terminated on Day 13. Mean QTc interval was statistically significantly prolonged (+6%; +15 msec) on Day 26 of the dosing phase in males administered 30/10 mg/kg/dose BID compared with controls. The prolongation in QTc for males was below the 10% increase or the threshold reported for canines exposed to therapeutic concentrations of drugs known to cause QT prolongation in humans.[8] Therefore, the QTc changes were considered physiologically unimportant, and thus not deemed to be adverse. Together, these data indicate that LOXO-305 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias in patients.

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

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

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

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

LOXO-305 showed no detectable inhibition (IC_{50} > 60 µM) of CYP1A2, CYP2B6, CYP2C19, and CYP2D6, and weak inhibition of CYP2C8, CYP2C9, and CYP3A4 in human liver microsomes. After pre-incubation of microsomes with LOXO-305 and nicotinamide adenine dinucleotide phosphate prior to addition of CYP450 probe substrate, the CYP3A4 inhibitory potency of LOXO-305 was increased, suggesting the potential for time-dependent inhibition of CYP3A4. Further kinetic evaluation confirmed that LOXO-305 is a time dependent inhibitor of CYP3A4.

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

In vitro LOXO-305 inhibited P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein (MATE) 1, and MATE2K. LOXO-305 did not inhibit organic anion transporter (OAT) 1 and weakly inhibited organic anion transporting

polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, OAT3, and bile salt exporter pump (BSEP).

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

1.4. Summary of Clinical Experience

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

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

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

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

As of the date of this protocol, 9 additional studies were ongoing in healthy volunteers and otherwise healthy volunteers with varying degrees of hepatic impairment (LOXO-BTK-20006, LOXO-BTK-20017, LOXO-BTK-20007, LOXO-BTK-20008, LOXO-BTK-20016, LOXO-BTK-20012, LOXO-BTK-20011, LOXO-BTK-20010, and LOXO-BTK-20009).

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 where, at the time of this protocol's development, 3 healthy volunteers were given 1 dose of 200 mg of LOXO-305, 12 healthy volunteers were given 200 mg of LOXO-305 on 2 separate days (1 of which was co-administered with itraconazole), each followed by a washout period, and 12 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days (2 of which were co-administered with rifampin), each followed by a washout period.

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

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

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

LOXO-BTK-20016 is a DDI study evaluating the effects of LOXO-305 on the PK of a CYP2C8 substrate (repaglinide) where, at the time of this protocol's development, 16 healthy volunteers were given 200 mg QD of LOXO-305 on 11 consecutive days (1 day of which was co-administered with oral repaglinide).

LOXO-BTK-20012 is a hepatic impairment study evaluating the PK profile of LOXO-305 in subjects with impaired hepatic function compared to matched-control healthy subjects, where, at the time of this protocol's development, 5 subjects were given a single dose of 200 mg LOXO-305.

LOXO-BTK-20010 is a DDI study evaluating the effects of LOXO-305 on the PK of a probe drug cocktail (200 mg caffeine [tablet], 40 mg omeprazole [capsule], and 10 mg warfarin [tablet]) where, at the time of this protocol's development, 12 healthy volunteers were given 1 dose of probe drug cocktail alone and 200 mg QD of LOXO-305 alone on 2 consecutive days.

LOXO-BTK-20009 is a formal food-effect crossover study evaluating the effects of food the PK of LOXO-305 where, at the time of this protocol's development, 20 healthy volunteers were given at least 1 dose of 200 mg of LOXO-305.

LOXO-BTK-20011 is a partially double-blind study to evaluate the effect of a single supratherapeutic dose of LOXO-305 on the QTc interval corrected for heart rate in healthy subjects compared to moxifloxacin and placebo, where, at the time of this protocol's development, 22 subjects had received 1 dose each of LOXO-305, moxifloxacin, and placebo and 1 subject had received 2 doses of either LOXO-305, moxifloxacin, or placebo.

1.4.1. Safety

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

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

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

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

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

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

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

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in Part 2 of the LOXO-BTK-20007 study (tenderness at left venipuncture site [x2], bruising

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

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

Adverse events reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20016 study (petechiae [x4], back pain, nausea, constipation, bilateral leg cramps, facial acne, epigastric abdominal pain, and brain fog) were all Grade 1 in severity, and petechiae [x4], constipation, bilateral leg cramps, epigastric abdominal pain, and brain fog were considered to be related to LOXO-305. All 11 AEs were reported by 7 subjects and all events resolved within 1 to 11 days (preliminary data on file at the time of this protocol's development).

There have been no TEAEs reported following LOXO-305 administration in healthy volunteers and volunteers with varying degrees of hepatic impairment in the LOXO-BTK-20012 and LOXO-BTK-20010 studies to date (preliminary data on file at the time of this protocol's development).

Adverse events reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20009 study (petechial rash and lightheadedness) were both Grade 1 in severity and petechial rash was considered to be related to LOXO-305. The 2 AEs were reported by 2 subjects and the events resolved within 1 to 6 days (preliminary data on file at the time of this protocol's development).

Adverse events reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20011 study (headache [x4], dry mouth, rash [various locations; x9], pyuria, bacteriuria, intermittent left eye pain, lightheadedness, muscle twitch – right shoulder, diarrhea, slight tremor – left hand, constipation, and nausea) were all Grade 1 in severity. All 23 TEAEs were reported by 10 subjects and all but 8 TEAEs of rash had resolved within 1 to 9 days (preliminary data on file at the time of this protocol's development).

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

1.4.2. Pharmacokinetics

As of September 30, 2020, PK data were available from 181 patients enrolled in the LOXO-BTK-18001 study. Steady-state PK parameters of LOXO-305 in these cancer patients could be derived from data collected on Cycle 1 Day 8 (Figure 1), and are shown in Table 1. These data show that LOXO-305 is absorbed after oral administration with a median time to maximum observed plasma concentration (t_{max}) of approximately 2 hours and low clearance (Table 1). Due to the limited sampling interval (0-8 hours), imputation for the 24-hour sample was made from Cycle 1, Day 8 predose sample, leading to an estimated plasma half-life of approximately 20 hours. Maximum observed plasma concentration and area under the plasma concentration-time curve (AUC) of LOXO-305 showed an increase proportional to dose (Figure 2). Following administration of the recommended Phase 2 dose (RP2D) 200 mg QD, mean trough plasma levels of LOXO-305 exceeded the concentration required for 96% inhibition of BTK in vitro (IC_{50} = CCI ng/mL, IC_{96} = CCI ng/mL). Further details may be found in the IB.[1]

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

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

Dose Level	N	C_{max} (ng/mL) Geo mean (%CV)	t_{max} (h) Median (min, max)	AUC_{0-8} (ng*h/ mL) Geo mean (%CV)	AUC_{0-24} (ng*h/mL) Geo mean (%CV)	CL/F (L/h) Geo mean (%CV)	$t_{1/2}$ (h) Geo mean (%CV)	Ratio AUC_{0-8} Day 8/Day 1 Geo mean (%CV)
25 mg QD	CCI							
50 mg QD								
100 mg QD								
150 mg QD								
200 mg QD								
250 mg QD								

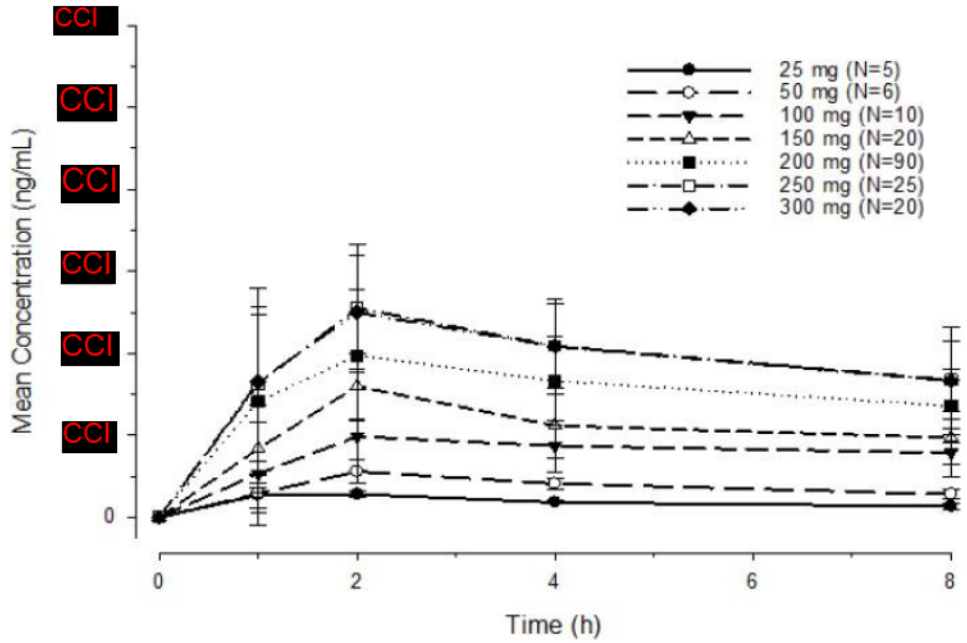
Dose Level	N	C_{max} (ng/mL) Geo mean (%CV)	t_{max} (h) Median (min, max)	AUC_{0-8} (ng*h/ mL) Geo mean (%CV)	AUC_{0-24} (ng*h/mL) Geo mean (%CV)	CL/F (L/h) Geo mean (%CV)	$t_{1/2}$ (h) Geo mean (%CV)	Ratio AUC_{0-8} Day 8/Day 1 Geo mean (%CV)
300 mg QD	CCI							

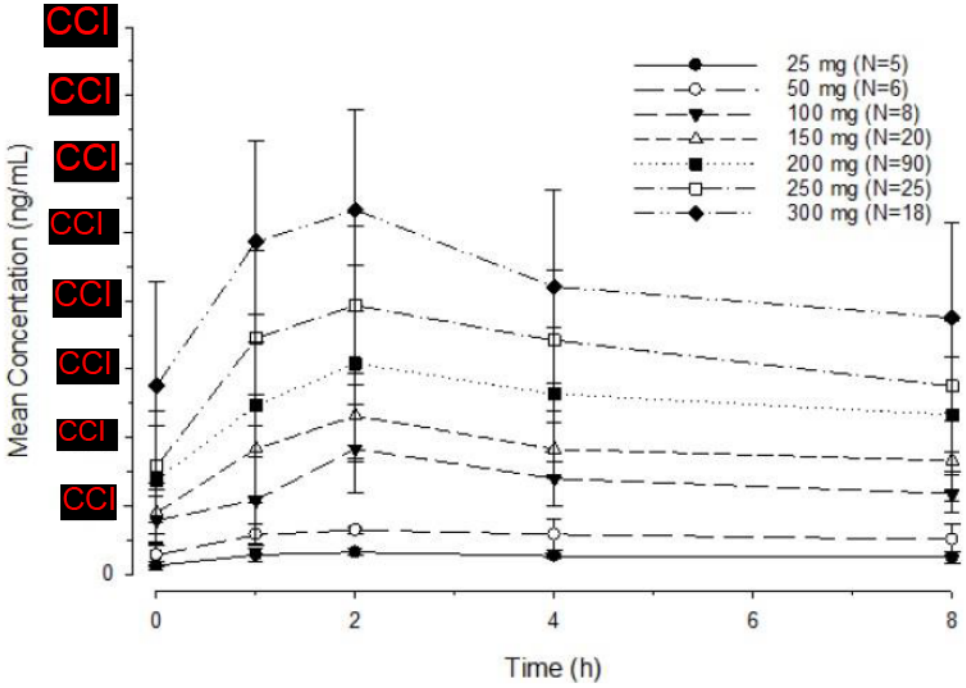
Abbreviations: AUC_{0-8} = area under the concentration-time curve from time 0 to 8 hours; AUC_{0-24} = area under the concentration-time curve from time 0 to 24 hours; CL/F = apparent oral clearance; C_{max} = maximum drug concentration; CV = coefficient of variation; Geo mean = Geometrical mean; N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

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

SDTM Transfer: September 30, 2020

CCI





SDTM Transfer: September 30, 2020

1.5. Study Rationale

This study is being conducted to provide information to develop dosing recommendations for LOXO-305 in subjects with renal impairment according to the Food and Drug Administration (FDA) Guidance for Industry.[9] Subjects with renal impairment may have compromised drug

disposition due to their renal disease and severity of disease. Results from this study will provide information on the safety, tolerability, and exposure of LOXO-305 in participants with renal impairment and participants with normal renal function.

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 consideration of this, subjects with renal impairment assessed as severe (estimated glomerular filtration rate [eGFR]: < 30 mL/min/1.73 m^2), along with matched-control healthy subjects with normal renal function, will begin enrolling into the study first. If a clinically relevant difference is observed in the PK of subject(s) with severe renal impairment compared to matched-control healthy subjects during continuous review of the safety and PK data, then subjects with renal impairment assessed as mild (60 ≤ eGFR < 90 mL/min/1.73 m^2) and/or moderate (30 ≤ eGFR < 60 mL/min/1.73 m^2), along with additional matched-control healthy subjects (if needed) will be enrolled, to determine the extent of the effect of varying severities of renal impairment on the PK of LOXO-305. Enrollment of subjects with mild and/or moderate renal impairment will only be initiated if deemed necessary by the Sponsor following the continuous review of safety and PK data from severe renal impairment subjects and their matched-control healthy subjects. If no clinically relevant effect on PK is observed, enrollment of mild and/or moderate subjects will not occur.

The PK profile of subjects with impaired renal function will be compared to subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2).

1.6. Risk Assessment

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-305 may be found in the IB.[1]

Single doses of 200 mg LOXO-305 were investigated in a study conducted in healthy volunteers (LOXO-BTK-20014) where 10 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days, each followed by a washout period. Two additional studies are ongoing in healthy volunteers (LOXO-BTK-20006 and LOXO-BTK-20017). 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 where, at the time of protocol development, 6 healthy volunteers were given 1 dose of 200 mg of LOXO-305, 12 healthy volunteers were given 200 mg of LOXO-305 on 2 separate days (1 of which was co-administered with itraconazole), each followed by a washout period, and 9 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days (2 of which were co-administered with rifampin), each followed by a washout period. LOXO-BTK-20017 is a SAD study evaluating the safety and tolerability of LOXO-305 at 300 mg, up to 600 mg, up to 800 mg, and up to 900 mg (if necessary) where, at the time of protocol development 6 healthy volunteers were given a single dose of 300 mg LOXO-305 and 6 healthy volunteers were given a single dose of 600 mg 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 were reported by 1 subject and resolved within 1 to 1.5 days (data on file at the time of protocol development). From preliminary AE data reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20006 study, all TEAEs (intermittent belching, bloating, insect bite, aphthous ulcer, nausea, intermittent diarrhea [x2], muscle twitch) were Grade 1 in severity and bloating, intermittent diarrhea, and intermittent belching were considered related to LOXO-305. All 7 AEs were reported by 3 subjects and all events resolved prior to EOT (data on file at the time of protocol development). From preliminary AE data reported following LOXO-305 administration in healthy volunteers in Cohort 1 of the LOXO-BTK-20017 study, there was one TEAE (headache) observed in the 300 mg LOXO-305 cohort which was Grade 1 in severity and considered related to LOXO-305. The event resolved within 2 hours (data on file at the time of protocol development).

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

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the PK profile of LOXO-305 in subjects with impaired renal function compared to matched-control healthy subjects.

2.1.2. Secondary Objective

The secondary objective of the study is to evaluate safety and tolerability of LOXO-305 in subjects with impaired renal function and matched-control healthy subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

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

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

In addition, a single blood sample will be collected predose to determine the unbound fraction (f_u) of LOXO-305 in plasma and, whenever possible, the following PK parameters will be calculated for unbound LOXO-305 using f_u: unbound C_{max} ($C_{max,u}$), unbound AUC_{0-t} ($AUC_{0-t,u}$), unbound AUC_{0-inf} ($AUC_{0-inf,u}$), unbound CL/F ($CL/F,_u$), and unbound V_z/F ($V_z/F,_u$).

2.2.2. Secondary Endpoints

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study is an open-label, nonrandomized, multi-center, single-dose, parallel-group study to determine the PK, safety, and tolerability of LOXO-305 administered orally at a dose of 200 mg to fasted adult males and females with impaired renal function and healthy subjects with normal renal function. Renal function will be classified based on the baseline eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation.[10] **Baseline eGFR will be obtained for all subjects (ie, subjects with renal impairment and matched-control healthy subjects) by taking the mean of the eGFR obtained from Screening and from historical values obtained within a 3-month period from Screening. If no historical eGFR value is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the 2 values will be used as the baseline eGFR for group assignment.** Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each group (ie, matched-control healthy subjects and subjects with severe renal impairment [and subjects with mild and/or moderate renal impairment, if they are enrolled]) to categorize subjects' renal impairment status. The eGFR based on CKD-EPI equation will be repeated at Check-in (Day -1) to confirm renal impairment status. For matched-control healthy subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the eGFR (based on the CKD-EPI equation), at the Investigator's (or designee's) discretion.

Subjects with severe renal impairment (Group 4), and matched-control healthy subjects with normal renal function (Group 1) will begin enrolling in the study first. Subjects will be recruited so that up to 8 subjects with severe renal impairment and up to 8 subjects with normal renal function are enrolled, with the goal of having at least 6 subjects with severe renal impairment and at least 6 matched-control healthy subjects complete the study.

Subjects will be enrolled within the following groups based on their eGFR values calculated using the CKD-EPI equation[10] at Screening and repeated at Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 1: Matched-control healthy subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2)
- Group 4: Subjects with severe renal impairment (eGFR: < 30 mL/min/1.73 m^2)

Continuous review of the safety data and PK data (if available) from up to 8 subjects with severe renal impairment and up to 8 matched-control healthy subjects with normal renal function will be conducted after these subjects have completed all study-related assessments through 72 hours (approximately 3 half-lives) postdose, at a minimum. The safety data will include AEs and serious AEs (SAEs), vital signs, physical examinations, ECGs, and clinical laboratory evaluations.

Following continuous review of the safety data and PK data from up to 8 subjects with severe renal impairment (Group 4) and up to 8 matched-control healthy subjects with normal renal function (Group 1), subjects with mild renal impairment (Group 2) and/or moderate renal impairment in (Group 3) may be enrolled if deemed necessary by the Sponsor. If no clinically

relevant effect on PK is observed in subjects in Group 1 and Group 4, enrollment of subjects in Group 2 and/or Group 3 will not occur.

If the Sponsor deems it necessary to enroll subjects with mild and/or moderate renal impairment, subjects will be recruited so that up to 8 subjects with mild renal impairment, up to 8 subjects with moderate renal impairment, and up to an additional 16 matched-control healthy subjects with normal renal function may be enrolled, with the goal of having at least 6 subjects with mild renal impairment and at least 6 subjects with moderate renal impairment and their matched-control healthy subjects complete the study. Enrollment and dosing for subjects in Group 2 and/or Group 3 may only occur after the safety and PK data for subject(s) in Group 1 and Group 4 through a minimum of 72 hours postdose are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Subjects will be enrolled within the following groups based on their eGFR values calculated using the CKD-EPI equation[10] at Screening and repeated at Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 2: Subjects with mild renal impairment ($60 \leq$ eGFR < 90 mL/min/1.73 m^2)
- Group 3: Subjects with moderate renal impairment ($30 \leq$ eGFR < 60 mL/min/1.73 m^2)

Baseline eGFR will be obtained for all subjects (ie, subjects with renal impairment and matched-control healthy subjects) by taking the mean of the eGFR obtained from Screening and from historical values obtained within a 3-month period from Screening. If no historical eGFR value is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the 2 values will be used as the baseline eGFR for group assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each group (ie, matched-control healthy subjects and subjects with severe renal impairment [and subjects with mild and/or moderate renal impairment, if they are enrolled]) to categorize subjects' renal impairment status. The eGFR based on CKD-EPI equation will be repeated at Check-in (Day -1) to confirm renal impairment status. For matched-control healthy subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the eGFR (based on the CKD-EPI equation), at the Investigator's (or designee's) discretion.

Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the completed renal impairment subject(s). Should another renal impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different renal impairment group. Each subject with normal renal function may be matched with up to 1 subject within each renal impairment group.

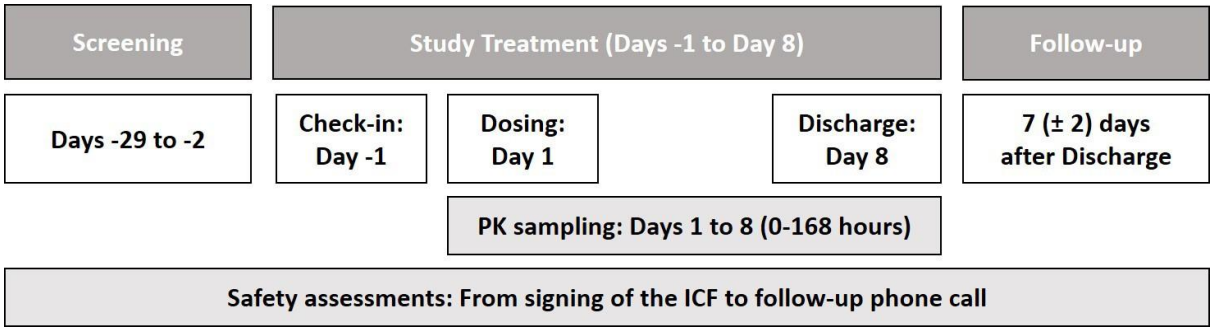
The schematic of the study design is displayed in Figure 3. The start of the study is defined as the date the first subject who is enrolled in the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned a dose of study drug; this definition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

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and will be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Subjects who are determined to be screen failures are permitted to be re-screened if the Investigator (or designee), with agreement from the Covance Medical Monitor and the Sponsor, feels that the subject may meet eligibility criteria upon re-screen. Re-screened subjects will be provided a new subject number.

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. Subjects will be dosed on Day 1. A follow-up phone call will occur for all subjects who received a 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 up to 46 days (Screening through follow-up phone call).

On the morning of Day 1, after at least an 8-hour fast, a single oral dose of 200 mg LOXO-305 will be administered with approximately 240 mL of water. No food will be allowed for up to 2 hours postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia in renally impaired subjects with diabetes. For instructions regarding food and water intake, refer to Section 6.2. Pharmacokinetic samples will be obtained through 168 hours postdose.

Figure 3: Study Design Schematic



ICF = Informed Consent Form; PK = pharmacokinetic.
Note: Single oral dose of LOXO-305 at 200 mg administered orally after at least an 8-hour fast.

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 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

A single-dose, parallel design is the standard design to investigate the PK of a drug in subjects with renal impairment. A parallel design is required to include subjects with renal impairment and matched-control healthy subjects with normal renal function. A single dose level of 200 mg LOXO-305 will be used because it is the dose intended for registration. The study will be open-label because the primary endpoints are objective rather than subjective.

Matched-control healthy subjects with normal renal function will be enrolled in this study to serve as a reference group for interpretation of the results. Based on nonclinical and clinical data, and the known PK profile of the compound, the duration of the treatment period is considered adequate to achieve the study objectives.[1] Oral doses were chosen because this is the intended clinical route of administration.

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 consideration of this, subjects with renal impairment assessed as severe (eGFR: < 30 mL/min/1.73 m^2), along with matched-control healthy subjects, will begin enrolling into the study first. If a clinically relevant difference is observed in the PK of subject(s) with severe renal impairment compared to matched-control healthy subjects during continuous review of the safety and PK data, then subjects with renal impairment assessed as mild ($60 \leq$ eGFR < 90 mL/min/1.73 m^2) and/or moderate ($30 \leq$ eGFR < 60 mL/min/1.73 m^2), along with additional matched-control healthy subjects (if needed) will be enrolled, to determine the extent of the effect of varying severities of renal impairment on the PK of LOXO-305. Enrollment of subjects with mild and/or moderate renal impairment will only be initiated if deemed necessary by the Sponsor following the continuous review of safety and PK data from severe renal impairment subjects and their matched-control healthy subjects (see Section 8.2). If no clinically relevant effect on PK is observed, enrollment of mild and/or moderate subjects will not occur.

3.3. Selection of Doses in the Study

LOXO-305

Single oral doses of 200 mg LOXO-305 will be evaluated as this dose level given QD has been chosen as the recommended Phase 2 dose for the ongoing global Phase 1/2 first-in-human study, LOXO-BTK-18001 (BRUIN Study). Doses of LOXO-305 from 25 mg QD to 300 mg QD have been evaluated in the ongoing global Phase 1/2 first-in-human study, LOXO-BTK-18001 (BRUIN Study) in patients with previously treated CLL/SLL or NHL with dose escalation up to 300 mg QD approved by the study's Safety Review Committee.

The available data demonstrate that LOXO-305 appears safe and well tolerated at these doses. At all evaluated doses, no dose-limiting toxicities have been identified in humans.[1]

4. SELECTION OF STUDY POPULATION

A total of up to 24 subjects with renal impairment (up to 8 subjects with severe impairment, and, if necessary, up to 8 subjects with moderate impairment, and/or up to 8 subjects with mild impairment, per eGFR using the CKD-EPI equation) and approximately 8 to 24 matched-control healthy subjects with normal renal function will be enrolled in the study with the goal of having at least 6 subjects from each renal impairment group enrolled in the study and at least 6 subjects with normal renal function complete the study. Healthy subjects will be matched demographically to renally impaired subjects as noted in Section 3.1.

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 BMI
6. Complete physical examination (Section 7.2.5)
7. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
8. Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, and supine blood pressure [BP] and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
9. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
10. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
11. Screens for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV) immunoglobulin M (IgM) core antibody, human immunodeficiency virus (HIV) antibody, and SARS-CoV-2 (COVID-19) via polymerase chain reaction (PCR) testing or antigen testing (or equivalent, as determined by the Investigator [or designee] with agreement from the Sponsor; Appendix 2)
12. Hemoglobin A1c (HbA1c) test (Appendix 2)
13. Screen for selected drugs of abuse, including cotinine (matched-control healthy subjects only) and alcohol (breath or urine test [Appendix 2])
14. eGFR (Appendix 2)
15. Pregnancy test (for female subjects only; Appendix 2)
16. Follicle-stimulating hormone (FSH) test (for post-menopausal female subjects only; Appendix 2)

17. Thyroid-stimulating hormone (TSH) test (Appendix 2)

4.2. Check-in Procedures (Day -1)

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

1. Review of inclusion/exclusion criteria
2. Interim medical history, including concomitant medication(s)
3. Weight and BMI
4. Abbreviated physical examination (Section 7.2.5)
5. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
6. Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, and supine BP and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
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 antigen testing (or equivalent, as determined by the Investigator [or designee] with agreement from the Sponsor; Appendix 2)
10. Screen for selected drugs of abuse, including cotinine (matched-control healthy subjects only) and alcohol (breath or urine test [Appendix 2])
11. eGFR (Appendix 2)
12. 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 Covance Medical Monitor will review medical history and all screening evaluations for potential subjects prior to Check-in (Day -1). Prior to dosing, the Covance Medical Monitor and 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), Covance Medical Monitor, 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:

All subjects:

1. Males, and females of non-childbearing potential, between 18 and 75 years of age, inclusive, at Screening.
2. Within BMI range 18.5 to 40.0 kg/m^2, inclusive.
3. In good health, except for additional specific inclusion criteria related to subjects with renal impairment, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, or clinical laboratory evaluations (Appendix 4) at Screening and/or Check-in (Day -1) as assessed by the Investigator (or designee).
4. Female subjects of non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to Day 1) or post-menopausal (defined as at least 12 months post-cessation of menses without an alternative medical cause). Post-menopausal status will be confirmed with a screening serum FSH level consistent with post-menopausal status per the laboratory's reference ranges. All female subjects must have a negative qualitative serum or negative qualitative urine pregnancy test (serum human chorionic gonadotropin; serum quantitative human chorionic gonadotropin tests may be used for confirmation as needed and post-menopausal subjects may be eligible for participation if the results of the qualitative serum pregnancy or qualitative urine pregnancy test are positive but the quantitative serum human chorionic gonadotropin results are within the laboratory's reference ranges for post-menopausal women) at Screening and Check-in (Day -1). Female subjects are required to refrain from donation of ova from Check-in (Day -1) until 6 months after Day 1.
5. Male subjects who are capable of fathering a child must agree to use 1 of the following methods of contraception:
    a. Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1), or
    b. If documentation is not available, male subjects must follow 1 of the contraception methods below from Day 1 through 6 months after Day 1:
        i. Male condom with spermicide, or
        ii. A male subject must ensure that their female partner meets 1 of the following criteria:
            1. intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®); or
            2. established use of oral, implanted, injected, transdermal, intravaginal, or hormonal method of contraception associated with inhibition of ovulation; or
            3. non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal

occlusion more than 6 months prior to Day 1 for male partner); or

4. be post-menopausal with amenorrhea for at least 1 year prior to Day 1 and FSH serum levels consistent with post-menopausal status.

Male subjects who practice true abstinence because of a lifestyle choice (ie, do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject is abstinent at the time of signing the ICF but becomes sexually active from Check-in (Day -1) through 6 months after Day 1, he must agree to use contraception as described above.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided from Check-in (Day -1) through 6 months after Day 1, unless the male subject uses a condom with spermicide. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) through 6 months after Day 1.

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

6. Able to understand and provide written informed consent.
7. Able to comply with all study procedures, including the 8-night stay at the CRU and follow-up phone call.

Additional inclusion criteria for matched-control healthy subjects only:

8. Matched to subjects with mild and/or moderate and/or severe renal impairment in sex, age (± 10 years), and BMI (± 20%). Note: Each matched-control healthy subjects may be matched with up to 1 subject within each renal impairment group.
9. Baseline eGFR ≥ 90 mL/min/1.73 m^2 at Screening and repeated at Check-in (Day -1) based on CKD-EPI equation.[10] A single assessment of actual creatinine clearance evaluated over a 24-hour urine collection may be used in place of the eGFR (based on the CKD-EPI equation) for matched-control healthy subjects, at the Investigator's (or designee's) discretion. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR range for a matched-control healthy subject (≥ 90 mL/min/1.73 m^2). Rechecks of eGFR or creatinine clearance values will be permitted up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation.

Additional inclusion criteria for subjects with renal impairment:

10. Considered to have mild, moderate, or severe renal impairment (of any etiology) that has been clinically stable (no acute episodes of illness due to deterioration in renal function) for at least 1 month prior to Screening per the Investigator (or designee), Sponsor, and Covance Medical Monitor and are likely to remain stable throughout EOS. To be classified as having renal impairment, subjects must have baseline eGFR based on the CKD-EPI equation[10] at Screening (and confirmed at Day -1) as follows:
    a. Severe renal impairment: < 30 mL/min/1.73 m^2

b. Moderate renal impairment: ≥ 30 and < 60 mL/min/1.73 m^2

c. Mild renal impairment: ≥ 60 and < 90 mL/min/1.73 m^2

Baseline eGFR will be obtained by taking the mean of the eGFR obtained from Screening and from historical values obtained within a 3-month period from Screening. If no historical eGFR value is available, a second Screening eGFR sample (using the CKD-EPI equation) will be taken during the Screening period (≥ 14 days apart) and the mean of the 2 values will be used as the baseline eGFR for group assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each group (ie, subjects with severe renal impairment [and subjects with mild and/or moderate renal impairment, if they are enrolled]) to categorize subjects' renal impairment status. The eGFR based on CKD-EPI equation will be repeated at Check-in (Day -1) to confirm renal impairment status. Rechecks of eGFR values will be permitted up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation.

11. Subject is not currently or has not previously been on hemodialysis, including peritoneal dialysis.
12. Currently on a stable medication regimen, defined as not starting new drug(s) or significantly changing drug dosage(s) within 30 days prior to Day 1. Concomitant medications administered within 30 days prior to Day 1 must be approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor. Subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on Day 1, unless approved by the Investigator (or designee) Covance Medical Monitor, and Sponsor.
13. Anemia secondary to renal disease will be acceptable if hemoglobin is ≥ 8 g/dL and anemia symptoms are not clinically significant. Must have ≥ 35,000 platelets.

4.4. Exclusion Criteria

The following will exclude potential subjects from the study:

All subjects:

1. History or presence of any of the following, deemed clinically significant by the Investigator (or designee), Covance Medical Monitor, and/or Sponsor:
    a. liver disease
    b. pancreatitis
    c. peptic ulcer disease
    d. intestinal malabsorption
    e. gastric reduction surgery
    f. history or presence of clinically significant cardiovascular disease:
        i. myocardial infarction or cerebrovascular thromboembolism within 6 months prior to Day 1
        ii. symptomatic angina pectoris within 6 months prior to Day 1

iii. New York Heart Association Class ≥ 2 congestive heart failure within 6 months prior to Day 1

iv. congenital prolonged QT syndrome

v. ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)

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

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

viii. clinically significant screening ECG abnormalities including, but not limited to:

1. complete left bundle-branch block
2. second-degree atrioventricular (AV) block, type 2, or third-degree AV block

2. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy and hernia repair will be allowed. Bariatric surgery and cholecystectomy will not be allowed.
3. Esophageal banding within 3 months prior to Check-in (Day -1) or required any other treatment for gastrointestinal bleeding within 6 months prior to Check-in (Day -1).
4. Clinically significant (as determined by the Investigator [or designee]) abnormal clinical laboratory results (hematology panel, UA, clinical chemistry panel [fasted at least 8 hours], excluding those further defined in inclusion criteria #9 and #10 above and exclusion criteria #28, #29, #30, #36 and #41 below) at Screening or Check-in (Day -1). Rechecks of clinically significant abnormal clinical laboratory results (excluding those further defined in inclusion criteria #9 and #10 above and exclusion criteria #28, #29, #30, #36 and #41 below) will be permitted up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the values fall within normal ranges or are stabilizing.
5. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator (or designee), and as confirmed by the Covance Medical Monitor and the Sponsor, or mentally or legally incapacitated or has significant emotional problems at the time of the Screening visit or expected during the conduct of the study.
6. Clinically significant abnormality, as determined by the Investigator (or designee), from physical examination at Screening and/or Check-in (Day -1).
7. Positive serologic test for HBsAg, HBV IgM core antibody, HCV antibody or HIV antibody at Screening. Subjects who are positive for HBV IgM core antibody or HCV antibody require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HBV core antibody or HCV antibody positive or for whom a PCR is unable to be obtained will not be eligible.
8. Positive PCR test or antigen testing (or equivalent, as determined by the Investigator [or designee] with agreement from the Sponsor) for COVID-19 at Screening or

Check-in (Day -1). Further details regarding COVID-19 testing (including procedures for subjects who test positive at any time throughout CRU confinement) are specified in a separate document.

9. 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.
10. 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 [matched-control healthy subjects only] 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), unless the positive drug screen is due to prescription drug use that is approved by the Investigator (or designee), Covance Medical Monitor, and Sponsor.
11. Consumption of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET.
12. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET.
13. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
14. Participation in any other investigational study drug trial where administration of any investigational drug occurred within 30 days or 5 half-lives (if known), whichever is longer, prior to Day 1.
15. 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 vitamin supplements, herbal products such as St. John's wort), strong CYP2C8 substrates, strong P-gp inhibitors, proton-pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, natural or herbal supplements, and hormone replacement therapy (HRT) within 14 days or 5 half-lives (if known), whichever is longer, prior to Day 1 and through EOT or ET, unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor or, if the subject is renally impaired, needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the Medical Monitor, Investigator (or designee), and Sponsor, and provided that the subject has been on a stable dose for a minimum of 30 days prior to Day 1.
16. History of a major surgical procedure within 30 days prior to Screening.
17. 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.
18. Poor peripheral venous access.
19. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
20. Receipt of blood products within 2 months prior to Check-in (Day -1).

21. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
22. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, and as confirmed by the Covance Medical Monitor and the Sponsor, within the 30 days prior to dosing and through EOT or ET.
23. Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the Investigator (or designee), and as confirmed by the Covance Medical Monitor and the Sponsor, might interfere with the study (eg, cimetidine) will be prohibited at least 2 weeks or 5 half-lives (if known), whichever is longer, prior to dosing and through EOT or ET.
24. Has completed or withdrawn from any other study investigating LOXO-305, and have previously received the investigational medicinal product within the last 30 days.

Additional exclusion criteria for matched-control healthy subjects:

25. QT interval corrected for heart rate using Fridericia's method (QTcF) of > 450 msec at Screening, Check-in (Day -1), or predose on Day 1. Rechecks of out-of-range QTcF values that are not clinically significant (as determined by the Investigator [or designee]) will be permitted up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 to confirm eligibility for study participation if the values fall within the range stated above.
26. Abnormal ECG findings deemed clinically significant by the Investigator (or designee) at Screening, Check-in (Day -1), or prior to dosing on Day 1.
27. 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. body temperature > 37.5°C;
    b. pulse rate < 50 or > 99 bpm;
    c. systolic BP < 89 or > 139 mmHg;
    d. diastolic BP < 50 or > 89 mmHg;
    e. oxygen saturation < 95% (room air).

    Rechecks of out-of-range values for these parameters (body temperature, pulse rate, BP, and oxygen saturation) that are not clinically significant (as determined by the Investigator [or designee]) will be permitted up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 to confirm eligibility for study participation if the values fall within the ranges stated above.
28. Abnormal 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 above the upper limit of the normal range that are not clinically significant (as determined by the Investigator [or designee]) will be permitted up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the values fall within normal ranges or are stable or normalizing as judged by the Investigator (or designee), and confirmed by the Covance Medical Monitor and the Sponsor.

29. Any clinically significant deviations from normal ranges in creatine kinase unless approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor. Rechecks of out-of-range creatine kinase values that are not clinically significant (as determined by the Investigator [or designee]) will be permitted up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the values are stable or normalizing as judged by the Investigator (or designee), and confirmed by the Covance Medical Monitor and the Sponsor.
30. Hemoglobin below the lower limit of normal range at Screening or Check-in (Day -1). Recheck of hemoglobin below the lower limit of normal range that is not clinically significant (as determined by the Investigator [or designee]) will be permitted up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the values are stable or normalizing as judged by the Investigator (or designee), and confirmed by the Covance Medical Monitor and the Sponsor.
31. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET.
32. Significant history or clinical manifestation of any allergic, dermatological, biliary, hepatic, gastrointestinal, renal, metabolic, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or heart failure), neurological, or psychiatric disorder (as determined by the Investigator [or designee]). Note: subjects with a history of appendectomy and/or hernia repairs will be acceptable.
33. History of diabetes mellitus (as evidenced by HbA1c ≥ 6.5% at Screening).
34. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).

Additional exclusion criteria for subjects with renal impairment:

35. QTcF value of > 450 msec for subjects with mild or moderate renal impairment or > 470 msec for subjects with severe renal impairment at Screening, Check-in (Day -1), or predose on Day 1. Rechecks of out-of-range QTcF values that are not clinically significant (as determined by the Investigator [or designee]) will be permitted up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 to confirm eligibility for study participation if the values fall within the range stated above.
36. Has rapidly fluctuating renal function; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as a difference in baseline and historical eGFR values that results in a change of renal impairment classification category over at least 3 months for subjects with historical eGFR values available at the time of Screening, or a difference in eGFR values that results in a change of renal impairment classification category for the 2 screening measurements (≥ 14 days apart) for subjects with no historical eGFR values available at the time of Screening.
37. Has had a renal transplant, a nephrectomy, or is a subject with a known history of nephrotic syndrome.
38. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter medications, vitamin supplements, natural or herbal supplements) from 14 days, or 5 half lives (if known), whichever is longer, prior to dosing and through EOT or ET, unless it is a prescription or over-the-counter medication or, needed to stabilize the subject's underlying medical condition (or

concurrent baseline conditions) which has been approved by the Investigator (or designee) with agreement from the Covance Medical Monitor and the Sponsor, and provided they have been on a stable regimen for at least 30 days prior to dosing and are able to withhold use for 2 hours predose and 4 hours postdose on the day of dose administration (Day 1) unless approved by the Investigator (or designee), with agreement from the Covance Medical Monitor and Sponsor.

39. Has required new medication for renal disease within 30 days prior to Check-in (Day -1).
40. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital signs at Screening, Check-in (Day -1), or prior to dosing on Day 1, including:
    a. Body temperature > 37.5°C;
    b. Pulse rate < 50 or > 99 bpm;
    c. Systolic BP < 89 or > 150 mmHg;
    d. Diastolic BP < 50 or > 95 mmHg;
    e. Oxygen saturation < 95% (room air).

    Rechecks of out-of-range values for these parameters (body temperature, pulse rate, BP, and oxygen saturation) that are not clinically significant (as determined by the Investigator [or designee]; based on the age and renal impairment status) will be permitted up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 to confirm eligibility for study participation if the values fall within the ranges stated above.
41. Values outside the normal ranges for creatine kinase, LFTs, amylase, and lipase may be acceptable as consistent with the subject's renal condition (if stable for 1 month prior to Screening), and if the Investigator (or designee), the Covance Medical Monitor, and the Sponsor feel that the results are not clinically significant (based on age and renal impairment status).
42. Smoking more than 10 cigarettes per day or equivalent (eg, e-vapor cigarette, pipe, cigar, chewing tobacco, nicotine patch, nicotine gum) throughout the confinement period of the study (EOT or ET); unable or being unwilling to refrain from the use of tobacco- or nicotine-containing products for 2 hours prior to dosing and 4 hours after dose administration on Day 1.
43. History of unstable diabetes mellitus (as evidenced by HbA1c ≥ 10.0% at Screening). Medications for the treatment of diabetes mellitus must be reviewed and approved by the Investigator (or designee), the Covance Medical Monitor, and the Sponsor.
44. History of cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin).
45. Recent history of paracentesis (within 30 days prior to Screening).

4.5. Subject Number and Identification

Subjects will be assigned into groups based on their level of renal function (Table 2) and will be assigned a number by CRU staff based on the assigned group. Assignment of numbers within each group will be in ascending order and no numbers will be omitted. Subject number

will consist of 6 digits in which the first set of 3 digits will identify the site and the second set of 3 digits will identify the subject (eg, 001-100). Subject numbers will be identified by group (eg, subject numbering will be as follows for Site 001):

- Group 1: Matched-control healthy subjects: 001-100 through 001-199
- Group 2: Subjects with mild renal impairment: 001-200 through 001-299
- Group 3: Subjects with moderate renal impairment: 001-300 through 001-399
- Group 4: Subjects with severe renal impairment: 001-400 through 001-499.

Subject numbers will be used on all study documentation. For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced. Replacement subjects will be assigned a subject number by adding 400 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-501 replaces Subject Number 001-101). Subjects who are determined to be screen failures are permitted to be re-screened if the Investigator (or designee), with agreement from the Covance Medical Monitor and the Sponsor, feels that the subject may meet eligibility criteria upon re-screen. Re-screened subjects will be provided a new subject number as defined above.

Table 2: Subject Group and Number of Subjects

Group	Description of Renal Function[a]	N
1	Matched Normal Renal Function	Up to 8 to 24[b]
2[b]	Mild Renal Impairment	Up to 8
3[b]	Moderate Renal Impairment	Up to 8
4	Severe Renal Impairment	Up to 8

[a] Renal function determined using the eGFR assessment.
[b] Group 2 and Group 3 (and additional matched-control healthy subjects) will only be enrolled if deemed necessary.

4.6. Removal of Subjects from Study Participation

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

- change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety
- occurrence of AEs
- occurrence of pregnancy
- intake of non-permitted concomitant medication that might affect subject safety or study assessments/objectives, etc.

Notification of withdrawal will immediately be made to the Study Monitor. In case of withdrawal, efforts will be made to perform all ET assessments (Appendix 4). The date the

subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's electronic Case Report Form (eCRF). All withdrawn subjects with AEs that are assessed as related to study drug and which are ongoing at ET may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator (or designee) and confirmed by the Sponsor.

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

- adverse events unknown to date with respect to their nature, severity, and/or duration
- increased frequency and/or severity and/or duration of known AEs
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancellation of drug development

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

4.7. Matching Process

A matched-control healthy subject will be matched to the completed renal impairment subject(s) (age [± 10 years], BMI [± 20%], and sex). An individual matched-control healthy subject may be matched with up to 1 subject within each renal impairment group (ie, to a maximum of 3 renally impaired subjects across the study [1 mild, 1 moderate, and 1 severe], but to no more than 1 subject in each impairment group). A listing of the matched subjects will be included in the Clinical Study Report.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drug (Table 3).

Table 3: Study Drug

Study Drug	LOXO-305
Form[a]	Tablet
Strength	100 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.

The tablets containing 100 mg LOXO-305 will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificate of Analysis. It will be provided in high-density polyethylene bottles and stored according to the instructions on the label.

Study drug 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

Subjects will receive a single dose of LOXO-305, given orally as two 100-mg tablets (200 mg total dose) in the morning on Day 1.

The study drug will be administered orally with approximately 240 mL of water. An additional 100 mL of water may be administered if needed. Doses will be preceded by a fast of at least 8 hours from food (not including water) and will be followed by a fast from food (not including water) for up to 2 hours postdose. Water will be restricted for 1-hour predose and 1-hour postdose, with the exception of water administered for dose administration. Glucose tablets may be administered as needed for treatment of hypoglycemia in renally impaired subjects with diabetes.

Each unit dose will be prepared by qualified CRU staff.

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

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

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

5.3. Randomization

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

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified CRU staff
- Immediately after oral dose administration, a visual inspection of the mouth and hands will be performed for each subject
- At each dose preparation occasion, a predose and postdose inventory of LOXO-305 will be performed

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of LOXO-305 tablets received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

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

At the completion of the study, all unused LOXO-305 tablets will be disposed of by the CRU, following the Sponsor’s written/emailed instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

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

All prescription medications and over-the-counter medications (including moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers [including herbal products such as St. John's wort], strong CYP2C8 substrates, strong P-gp inhibitors, proton-pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, vitamin supplements, natural or herbal supplements, medications that would significantly alter eGFR [eg, cimetidine], and HRT) are prohibited for 14 days or 5 half-lives (if known), whichever is longer, prior to Day 1 and through EOT or ET, unless deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor or, if the subject is renally impaired, needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as described below.

For renally impaired subjects, the use of prescription and over-the-counter medications that are needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable by the Covance Medical Monitor, Investigator (or designee), and Sponsor are allowed, provided that the subject has been on a stable dose for a minimum of 30 days prior to Day 1. Renally impaired subjects must be able to withhold the use of these medications for 2 hours predose and 4 hours postdose on Day 1, unless approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor. Short-term medication adjustments may be made upon consultation with the Covance Medical Monitor, Investigator (or designee), and Sponsor per the Medical Responsibility Plan. The use of additional medications is to be avoided from 14 days prior to Day 1 until EOT or ET unless required to treat an AE. All concomitant medications needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) will be reviewed by the Covance Medical Monitor, Investigator (or designee), and Sponsor prior to subject approval.

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 Covance Medical Monitor, 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

Matched-control healthy 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. Renally impaired subjects are required to refrain from the use of tobacco- and nicotine-containing products within 2 hours prior to dosing and for 4 hours postdose.

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

Consumption of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET will not be allowed.

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

While confined at the CRU, subjects will receive a standard diet at scheduled times that do not conflict with other study-related activities. Water will be restricted for 1-hour predose and 1-hour postdose, with the exception of water administered for dose administration. Glucose tablets may be administered as needed for treatment of hypoglycemia in renally impaired subjects with diabetes.

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 plasma concentrations of LOXO-305 and unbound LOXO-305 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 and unbound LOXO-305 samples will be provided in a separate Laboratory Manual. The number of blood samples and total blood volume required for PK testing and unbound LOXO-305 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. The concentrations of total and unbound LOXO-305 will be determined in a sample of predose plasma fortified with a known concentration of LOXO-305. The f_u will be calculated based on total and unbound LOXO-305 levels. Samples of plasma may be analyzed for exploratory analyses of metabolites. If such analyses are conducted, the results will be reported separately by the Sponsor.

7.2. Safety and Tolerability Assessments

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

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

- dosing
- PK blood sampling
- vital sign measurements
- 12-lead ECGs
- 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 for LOXO-305 for additional safety information. [1]

7.2.2. Clinical Laboratory Evaluations

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

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

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

A urine drug screen for selected drugs of abuse (including cotinine [matched-control healthy subjects only] and alcohol [urine or breath test]) will be performed at Screening and repeated at Check-in (Day -1) for all subjects. A serum qualitative or urine qualitative pregnancy test (female subjects only [quantitative serum human chorionic gonadotropin tests may be used for confirmation as needed and post-menopausal subjects may be eligible for participation if the results of the qualitative serum pregnancy or qualitative urine pregnancy test are positive but the quantitative serum human chorionic gonadotropin results are within the laboratory's reference ranges for post-menopausal women]) and an FSH test (post-menopausal female subjects only) will be performed at the timepoints specified in Appendix 4.

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

7.2.3. Vital Signs

Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, 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 heart rate, 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

A total of up to 24 subjects with renal impairment (up to 8 subjects with severe impairment, and, if necessary, up to 8 subjects with moderate impairment, and/or up to 8 subjects with mild impairment, per eGFR using the CKD-EPI equation) and approximately 8 to 24 matched-control healthy subjects with normal renal function will be enrolled in the study with the goal of having at least 6 subjects from each renal impairment group enrolled in the study and at least 6 subjects with normal renal function complete the study. The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and was not based on power calculations to detect statistically significant differences among groups. This number is considered a sufficient sample size to evaluate the PK of LOXO-305 under various degrees of renal function.

8.2. Interim Analysis

Subjects with renal impairment assessed as severe, along with matched-control healthy subjects, will begin enrolling in the study first. Continuous review of the safety data and PK data (if available) from up to 8 subjects with severe renal impairment and up to 8 matched-control healthy subjects with normal renal function will be conducted after these subjects have completed all study-related assessments through 72 hours (approximately 3 half-lives) postdose, at a minimum. The safety data will include AEs and SAEs, vital signs, physical examinations, ECGs, and clinical laboratory evaluations.

If a clinically relevant difference is observed in the PK of subject(s) with severe renal impairment compared to matched-control healthy subjects during continuous review of the safety and PK data, then subjects with renal impairment assessed as mild ($60 \leq$ eGFR < 90 mL/min/1.73 m^2) and/or moderate ($30 \leq$ eGFR < 60 mL/min/1.73 m^2), along with additional matched-control healthy subjects (if needed) will be enrolled, to determine the extent of the effect of varying severities of renal impairment on the PK of LOXO-305. Enrollment of subjects with mild and/or moderate renal impairment will only be initiated if deemed necessary by the Sponsor following the continuous review of safety and PK data from severe renal impairment subjects and their matched-control healthy subjects. If no clinically relevant effect on PK is observed, enrollment of mild and/or moderate subjects will not occur.

Enrollment and dosing for remaining subjects in Group 2 and/or Group 3 may only occur after the data for Group 1 and Group 4 are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Subjects will be recruited for Group 2 and/or Group 3 so that up to 8 subjects with mild renal impairment, up to 8 subjects with moderate renal impairment, and up to an additional 16 matched-control healthy subjects with normal renal function may be enrolled, with the goal of having at least 6 subjects with mild renal impairment and at least 6 subjects with moderate renal impairment and their matched-control healthy subjects complete the study.

Teleconferences will occur as needed between the Covance Medical Monitor, Investigator (or designee), and Sponsor to discuss PK, safety, and tolerability data.

8.3. Analysis Populations

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

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

8.4. Pharmacokinetic Analysis

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

C_{max}	maximum observed plasma concentration
t_{max}	time to maximum observed plasma concentration
AUC_{0-t}	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 hour 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}
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
$t_{1/2}$	apparent plasma terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (2)/λ_Z
CL/F	apparent systemic clearance
V_z/F	apparent volume of distribution during the terminal phase
MRT	mean residence time
f_u	unbound fraction, calculated as unbound concentration divided by total concentration

The f_u value determined for each subject will be used to calculate the following unbound LOXO-305 PK parameters for each individual subject:

$C_{max,u}$	Unbound C_{max}, calculated as C_{max}*f_u
$AUC_{0-t,u}$	Unbound AUC_{0-t}, calculated as AUC_{0-t}*f_u

$AUC_{0\text{-}inf,u}$	Unbound $AUC_{0\text{-}inf}$, calculated as $AUC_{0\text{-}inf}*f_u$
$CL/F,_u$	Unbound CL/F, calculated as Dose/$AUC_{0\text{-}inf,u}$
$V_z/F,_u$	Unbound V_z/F, calculated as $CL/F,_u/\lambda_Z$

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

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

Pharmacokinetic analysis will use actual times as recorded on the eCRF. All statistical analyses will be performed using SAS® Version 9.4 or greater. More details on the analyses will be included in the SAP.

8.4.1. Descriptive Analysis

Plasma concentrations and PK parameters will be summarized by renal function classification with descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum). In addition, summary statistics for unbound LOXO-305 will be tabulated by renal function classification.

8.4.2. Statistical Methodology

The primary analysis planned for this study is to evaluate the PK of LOXO-305 after a single dose in subjects with renal impairment compared to subjects with normal renal function.

Paired t-tests will be performed to assess the differences in PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}) between each renal impairment group versus the corresponding matched-control healthy group with respect to 1 to 1 matching. The analysis will be based on the natural log (ln)-transformed PK parameters. Geometric mean ratios and their corresponding 90% confidence intervals (CIs) will be calculated using the exponentiation of the mean difference and the CIs obtained for the difference in mean between each renal impairment group and the matching healthy control group.

In addition, an analysis of covariance (ANCOVA) will be performed on the ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. The ANCOVA model will contain a categorical factor of population for subjects with varied-degree renal impairment (severe, moderate, and mild) and matched-control healthy subjects, a categorical covariate (sex), and continuous covariates (age and BMI). Ratios of least squares means and 90% CIs will be calculated using the exponentiation of the difference between renal function cohort least squares means from the ANCOVA analyses on the ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. In addition, an ANCOVA will be performed on the ln-transformed $AUC_{0\text{-}t,u}$, $AUC_{0\text{-}inf,u}$, and $C_{max,u}$.

The relationship between LOXO-305 PK parameters (ie, C_{max} and AUC) and measures of renal function (such as eGFR and creatinine clearance) may be explored using a linear regression approach or other methods. The effect of covariates such as age, BMI, and sex may be investigated.

The specific procedures will be documented in the SAP.

8.5. Safety Analysis

All safety assessments, including AEs, SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and 12-lead ECGs, will be tabulated, and summarized where possible, using descriptive methodology by renal function group and, 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 World Health Organization (WHO) Drug Dictionary (WHO Drug Global B3, September 2019). Adverse events will be coded using Medical Dictionary for Regulatory Activities Version (MedDRA) 22.1 (or higher). The incidence of AEs for each renal function group (matched control healthy subjects, mild, moderate, and severe) 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, with a breakdown by renal function group.

8.6. Data Handling and Record Keeping

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

The Data Management Plan will be approved by the Sponsor.

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

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

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

8.7. Quality Control and Quality Assurance

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

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

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

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

9.2. Site Initiation Visit/Investigator Meeting

Prior to the start of the clinical study, the representative(s) of the Sponsor and/or Sponsor will meet with the Investigator (or designee) and appropriate CRU staff to familiarize the Investigator (or designee) and site 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

Covance (on behalf of the Sponsor) will designate Study Monitors who will be responsible for monitoring this clinical trial. Covance's Study Monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. It is essential that Covance's Study Monitors have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, Covance's Study Monitors 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 Covance's Study Monitors.

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), and Applications for FDA Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable International Council for Harmonisation Guidelines, are commonly known as Good Clinical Practices, which are consistent with the Declaration of Helsinki.

9.9. Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

10. REFERENCES

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

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

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

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

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

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

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

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

9. Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [Internet]. Food and Drug Administration; 2010 [cited 2020 Jan 27]. Available from: https://www.fda.gov/media/78573/download

10. Levey AS, Stevens LA, et al. The CKD-EPI Creatinine Equation [Internet]. 2009 [cited 2021 Feb 15]. Available from: http://nephron.com/epi_equation

11. APPENDICES

Appendix 1: Adverse Event Reporting

Adverse Events

Definition of Adverse Events

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

The following are all AEs:

- unfavorable changes in general condition
- subjective or objective signs/symptoms
- concomitant diseases or accidents
- clinically significant adverse changes in laboratory parameters observed in a subject during a clinical study.

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

Categorization of Adverse Events

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

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

Note: Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.
* Instrumental ADL refer to preparing meals, shopping for groceries, or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

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

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

Pregnancy

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed through End of Study 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 Day 1 should be reported by the Investigator (or designee) via email to Covance or the Sponsor's Clinical Safety Representative within 24 hours of being notified. Covance or the Sponsor's Clinical Safety Representative will then forward the Pregnancy Form to the Investigator (or designee) for completion.

email: SAEIntake@Covance.com

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and ET study procedures will be performed. The subject or partner should be followed by the Investigator (or designee) until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator (or designee) should notify Covance or the Sponsor's Clinical Safety Representative. At the completion of the pregnancy, the Investigator (or designee) will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (SAE; 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 (or designee) immediately if they discover their sexual partner is pregnant. In this instance, the partner must provide written consent before pregnancy information can be collected. When a Clinical Research Unit (CRU) becomes aware that the female partner of a male subject is pregnant, they are to contact the Investigator (or designee) immediately (within 24 hours of the CRU staff becoming aware of the event) in addition to notifying Covance or the Sponsor's Clinical Safety Representative via email.

All pregnancies should be recorded on the AE electronic Case Report Form (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 Food and Drug Administration [FDA] definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

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

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

Unexpected Adverse Drug Reaction

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

Reporting

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

Within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported, and within 24 hours of any SAE (regardless of whether the event is assessed as related or unrelated to study drug) being first recognized or reported, Covance or the Sponsor’s Clinical Safety Representative will be notified by the Investigator (or designee) in writing using the following email address:

email: SAEIntake@Covance.com

To report the SAE, the completed report form should be sent by email to Covance or the Sponsor’s Clinical Safety Representative within 24 hours of awareness. Incoming reports are

reviewed during normal business hours. Additional reporting instructions and the SAE Report Form are provided in the Study Manual.

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

Appendix 2: Clinical Laboratory Evaluations

<table>
<tr><th>Clinical Chemistry Panel (Fasted):</th><th>Hematology Panel:</th><th>Other Tests:</th></tr>
<tr><td>Alanine aminotransferase
Albumin
Alkaline phosphatase
Amylase
Aspartate aminotransferase
Bilirubin (direct and total)
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatine kinase
Creatinine[f]
Glucose
Iron
Lipase
Magnesium
Phosphorus
Potassium
Sodium
Total protein
Triglycerides
Uric acid</td><td>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</td><td>Hemoglobin A1c[b]
Thyroid-stimulating hormone[b]
Estimated glomerular filtration rate (eGFR)[a,d,f]
SARS-CoV-2 (COVID-19) test</td></tr>
<tr><td></td><td></td><td>Coagulation Parameters:</td></tr>
<tr><td></td><td></td><td>Partial thromboplastin time
Prothrombin time
International normalized ratio</td></tr>
<tr><td></td><td></td><td>Serology:[b]</td></tr>
<tr><td></td><td></td><td>Human immunodeficiency virus antibody
Hepatitis B surface antigen
Hepatitis B virus IgM core antibody
Hepatitis C virus antibody</td></tr>
<tr><td></td><td></td><td>For Female Subjects only:</td></tr>
<tr><td></td><td>Urinalysis:</td><td rowspan="3">Pregnancy test (serum qualitative or urine qualitative, serum quantitative human chorionic gonadotropin tests may be used for confirmation if needed and post-menopausal subjects may be eligible for participation if the results of the qualitative serum pregnancy or qualitative urine pregnancy test are positive but the quantitative serum human chorionic gonadotropin results are within the laboratory's reference ranges for post-menopausal women)[c]
Follicle-stimulating hormone (post-menopausal female subjects only)[b]</td></tr>
<tr><td>Urine Drug Screen:[a]</td><td>Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic examination including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or occult blood is positive)</td></tr>
<tr><td>Including but not limited to the following:
Alcohol (ethanol)[e]
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine (healthy subjects only)</td></tr>
</table>

a. Performed at Screening and Check-in (Day -1) only.
b. Performed at Screening only.
c. Performed at Screening, Check-in (Day -1), and Day 7/Early Termination (ET) only.
d. Calculated using the using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
e. Urine or breath test.
f. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from Screening and from historical values obtained within a 3-month period from Screening. If no historical eGFR value is available, a second Screening eGFR sample (using the CKD-EPI equation) will be taken during the Screening period (≥ 14 days apart) and the mean of the 2 values will be used as the baseline eGFR for group assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each group (ie, subjects with severe renal impairment [and subjects with mild and/or moderate renal impairment, if they are enrolled]) to categorize subjects' renal impairment status. The eGFR based on CKD-EPI equation will be repeated at Check-in (Day -1) to confirm renal impairment status. For matched-control healthy subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the eGFR (based on the CKD-EPI equation), at the Investigator's (or designee's) discretion.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject:

Purpose	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	4	1	4
Hemoglobin A1c	4	1	4
Pharmacokinetic (PK) Sampling	4	20	80
Unbound Drug PK Sampling	4	1	4
Clinical Laboratory Evaluations:			
Hematology	4	5	20
Clinical Chemistry[a]	4	6[b]	24
Coagulation Parameters	3	5	15
Serum Pregnancy Test (females only)	2	3	6
Serum Follicle-stimulating Hormone Test (postmenopausal females only)	2	1	2
Thyroid-stimulating Hormone	2	1	2
		Total:	**161 mL**

[a] Estimated glomerular filtration rate will be assessed as part of the clinical chemistry sample.
[b] A second Screening eGFR sample may be taken during the Screening period if needed for baseline eGFR assessment.

Note: Although the total maximum volume to be analyzed is anticipated to be approximately 161 mL, due to the variability in sampling requirements at different laboratories, the total volume of blood collected from each subject may vary.

Appendix 4: Schedule of Assessments

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Study Conduct		CRU Discharge/ EOT or ET[t]	Follow-up Phone Call (EOS)
			Day 1	Days 2 to 7	Day 8	7 (± 2) days post EOT or ET[v]
Confined to the CRU		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			X	
12-Lead ECG[e]	X	X	X	X	X	
Vital Signs[f]	X[g,h]	X[g,h]	X[h]	X	X[g,h]	
HDYF? Inquiry[i]	X	X	X	X	X	X
AEs/SAEs[j]	X	X	X	X	X	X
LOXO-305 Dose[k]			X			
CCI						
Clinical Laboratory Evaluations[n]	X	X		X[u]	X[u]	
COVID-19 Test[o]	X	X				
eGFR	X	X				
Hepatitis and HIV Screen	X					
HbA1c Test	X					
Drug Screen[p]	X	X				
Prior and Concomitant Medications[q]	X	X	X	X	X	X
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-CoV-2; CRF = Case Report Form; CRU = Clinical Research Unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; ICF = Informed Consent Form; PK = pharmacokinetic; SAE = serious adverse event; TSH = thyroid-stimulating hormone; UA = urinalysis.

a. For details on study procedures, see Section 7.
b. Interim medical history only.
c. Height collected at Screening only; BMI based on Screening height.
d. A complete physical examination will be performed at Screening and EOT (Day 8, 168 hours postdose) or ET. An abbreviated physical examination will be performed at Check-in (Day -1).
e. 12-lead ECGs will be obtained at Screening and Check-in (Day -1), Day 1 (predose and 3 hours postdose), Day 3 (48 hours postdose), and EOT (Day 8, 168 hours postdose) or ET. When scheduled at the same time as blood draws, 12-lead ECGs will be collected after the subject has rested in the supine position for at least 10 minutes and will be obtained prior to and as close

as possible to the scheduled blood draws. The allowed sampling window for 12-lead ECGs is ±30 minutes from the nominal timepoint for all postdose 12-lead ECGs and no less than 10 minutes prior to dosing for predose 12-lead ECGs.

f. Vital sign measurements (supine BP and pulse rate) will be obtained at Screening, Check-in (Day -1), Day 1 (predose, 2 hours after dosing), daily on Days 2 through 7 (24, 48, 72, 96, 120, and 144 hours postdose), and at EOT (Day 8, 168 hours postdose) or ET. When scheduled at the same time as blood draws, vital sign measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes. The allowed sampling window for vital sign measurements is ±30 minutes from the nominal timepoint for all postdose vital sign measurements and no less than 10 minutes prior to dosing for predose vital sign measurements.
g. Body temperature and respiratory rate will be obtained at Screening, Check-in (Day -1), and at EOT (Day 8, 168 hours postdose) or ET.
h. Oxygen saturation measured by pulse oximetry will be measured at Screening, Check-in (Day -1), predose on Day 1, and at EOT (Day 8, 168 hours postdose) or ET. The allowed sampling window for oxygen saturation measurements is ±30 minutes from the nominal timepoint for all postdose oxygen saturation measurements and no less than 10 minutes prior to dosing for predose oxygen saturation measurements.
i. A HDYF? inquiry will be performed at Screening (after the ICF is signed), at Check-in (Day -1), at each postdose vital sign measurements, and at an appropriate time for all other days.
j. Adverse events and SAEs will be collected beginning at informed consent. Adverse events will be recorded throughout the study (ie, from signing of the ICF until EOS, or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed by the Investigator [or designee]) as related to study procedures, or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug. From EOT or ET through EOS, only AEs assessed as related to study drug are to be recorded. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.
k. On Day 1, LOXO-305 will be dosed in the morning. LOXO-305 will be administered following a fast of at least 8 hours predose and up to 2 hours postdose.

CCI

n. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and UA will be performed at Screening, Check-in (Day -1), Day 2 (24 hours postdose), Day 5 (96 hours postdose), and Day 7 (144 hours postdose), if the subject completes the study (EOT) or on the day of ET. Clinical laboratory evaluations will be performed on the day prior to subject release from the CRU if the subject completes the study (EOT). Clinical laboratory evaluations will be performed on the day of subject release from the CRU if the subject terminates early (ET). At ET or the day before EOT (Day 7), subjects are not required to be fasted prior to clinical laboratory evaluations. The allowed sampling window for clinical chemistry panel, coagulation parameters, hematology panel, and UA is within the same day that they are required.
o. Testing for COVID-19 will be conducted at a minimum of 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 antigen testing (or equivalent, as determined by the Investigator [or designee] with agreement from the Sponsor).
p. Drugs of abuse urine test, including cotinine (matched-control healthy subjects only) and alcohol (urine or breath test). 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 30 days prior to Day 1 for prescription medications (for renal impairment subjects only), and for all prescription and over-the-counter medications, those taken 14 days or 5 half-lives (if known), whichever is longer, prior to Day 1 will be recorded on the subject's electronic CRF.
r. Female subjects only. Performed at Screening, Check-in (Day -1), and Day 7 (144 hours postdose), if the subject completes the study (EOT) or on the day of ET. Pregnancy tests will be performed on the day prior to subject release from the CRU if the subject completes the study (EOT).
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 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 (Day 8) or ET. Clinical laboratory results (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 is contacted 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.

Appendix 5: Protocol Amendment Summary of Changes

Protocol Version 2.0 (dated 17 February 2021) incorporated the following changes in Protocol Version 1.0 (dated 29 October 2020):

- A reference to the CKD-EPI equation to be used to calculate estimated glomerular filtration rate has been added.
- The version of the Investigator Brochure referenced has been updated and the Protocol has been updated based on this and data from ongoing clinical studies.
- Allowance of qualitative urine pregnancy testing, in addition to serum qualitative pregnancy testing.
- Clarification that post-menopausal female subjects requiring a quantitative serum human chorionic gonadotropin test may be eligible for participation in the study if the values fall within the normal ranges for post-menopausal females.
- Exclusion criterion #35 has been updated to exclude patients with severe renal impairment with a QT interval corrected for heart rate using Fridericia's method of > 470 msec, instead of > 480 msec.
- An additional electrocardiogram assessment has been added at 3 hours postdose on Day 1.
- Clarification that polymerase chain reaction or antigen testing for SARS-CoV-2 (COVID-19) can be used to confirm there is no active infection.