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

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A wholly owned subsidiary of Eli Lilly and Company
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Study Site:
Multiple Sites

Sponsor Signatory:
PPD

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Multiple Investigators

SPONSOR APPROVAL

I have read the protocol and approve it:

07-Oct-20 | 13:40:45 PDT

Date

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 Hepatically 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 hepatic 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 hepatic 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 mild, moderate, or severe impaired hepatic function and healthy subjects with normal hepatic function. Hepatic function will be classified based on the Child-Pugh (CP) classification of hepatic impairment.

Subjects will be recruited in this study so that up to 24 subjects with hepatic impairment (up to 8 subjects with mild impairment, up to 8 subjects with moderate impairment, and up to 8 subjects with severe impairment, per CP classification – assessed at Screening and verified at Check-in [Day -1]) and 8 to 24 subjects with normal hepatic function are enrolled, with the goal of having at least 6 subjects from each hepatic impairment group per CP classification and at least 6 subjects with normal hepatic function complete the study. Hepatically impaired subjects will be assigned to groups according to CP scores at Check-in (Day -1) to ensure stability of hepatic impairment and subject safety, as determined by the Investigator (or designee). Subjects will be enrolled within the following groups based on their CP score at Screening and Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 1: Matched-control healthy subjects with normal hepatic function;
- Group 2: Subjects with mild hepatic impairment (CP Class A, score of 5 or 6);
- Group 3: Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9);
- Group 4: Subjects with severe hepatic impairment (CP Class C, score of 10 to 15);

A parallel-design strategy will be adopted for the hepatic impairment groups, with interim reviews of safety data after the first 2 subjects from Group 2 (mild hepatic impairment subjects) and Group 3 (moderate hepatic impairment subjects) and matched-control healthy subjects are enrolled and have completed all study-related assessments including the follow-up phone call. The safety data will include adverse events (AEs) and serious AEs (SAEs),

vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory evaluations. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing. If available, PK data and matched-control healthy subject data may also be used during the interim review.

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 hepatic impairment subject(s). Should another hepatic 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 hepatic impairment group. Each subject with normal hepatic function may be matched with up to 1 subject within each hepatic impairment group.

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

Number of Subjects

A total of up to 24 subjects with hepatic impairment (up to 8 subjects with mild impairment, up to 8 subjects with moderate impairment, and up to 8 subjects with severe impairment, per CP classification) and approximately 8 to 24 matched-control healthy subjects with normal hepatic function will be enrolled in the study with the goal of having at least 6 subjects from each hepatic impairment group per CP classification and at least 6 subjects with normal hepatic function complete the study. Of these hepatic impairment subjects enrolled per CP category, enrollment will also aim to have at least 4 subjects meet severe hepatic impairment criteria per the National Cancer Institute's Organ Dysfunction Working Group (NCI-ODWG) classification, at least 4 subjects meet moderate hepatic impairment criteria per NCI-ODWG classification, and at least 4 subjects meet mild hepatic impairment criteria per NCI-ODWG classification. Subjects who withdraw or drop out of the study may be replaced if deemed necessary by the Sponsor.

Main Criteria for Inclusion

Male subjects and female subjects of nonchildbearing 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 hepatic impairment, based on medical history, physical examination findings, vital sign measurements, ECG, and clinical laboratory evaluations at Screening and Check-in (Day -1), as determined by the Investigator (or designee).

Investigational Medicinal Products, Dose, and Mode of Administration

LOXO-305 will be supplied by the Sponsor as 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 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.

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.

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 (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_d/F ($V_z/F_{,u}$).

Safety:

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

Statistical Methods

The primary analysis planned for this study is to evaluate the PK of LOXO-305 after a single dose in subjects with mild, moderate, or severe hepatic impairment, compared to subjects with normal hepatic function. To evaluate the effect of hepatic function group on the PK of a single dose of LOXO-305, paired t-tests will be performed for each hepatic impairment group (by CP classification) versus the normal group with respect to 1-to-1 matching.

In addition, an analysis of covariance (ANCOVA) will be performed on the natural log (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 hepatic impairment (severe, moderate, and mild by CP classification) and healthy matched-control subjects, a categorical covariate (sex), and continuous covariates (age and BMI). Ratios of least squares means and 90% confidence intervals will be calculated using the exponentiation of the difference between hepatic 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 natural log (ln)-transformed unbound AUC_{0-t}, unbound AUC_{0-inf}, and unbound C_{max}. Similar ANCOVA analysis will be applied for evaluating the effect of hepatic function group by NCI-ODWG classification.

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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
bpm	beats per minute
BSEP	bile salt exporter pump
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
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
CP	Child-Pugh
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
EMA	European Medicines Agency
EOS	End of Study

EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
f_u	fraction unbound
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDYF?	How Do You Feel?
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HRT	hormone-replacement therapy
IB	Investigator's Brochure
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
NCI-ODWG	National Cancer Institute-Organ Dysfunction Working Group
NHL	non-Hodgkin lymphoma
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
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 (IMP), LOXO-305.[1]

1.1. Background

LOXO-305 (also known as LY3527727) is a selective inhibitor of the Bruton's tyrosine kinase (BTK) being developed by Loxo Oncology. LOXO-305 is distinct from the approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) in several important ways including on the basis of its selectivity, favorable absorption, distribution, metabolism, and excretion properties, and non-covalent binding mode.[2] The non-covalent binding mode of LOXO-305 is unaffected by BTK C481 substitutions, a common mechanism of drug resistance described for all available covalent inhibitors.[3,4,5,6,7] These features enable LOXO-305 dosed orally at 100 mg and higher once daily (QD) to achieve pharmacokinetic (PK) exposures that exceed the concentration required for 90% inhibition (IC_{90}) of BTK-wild type and BTK C481 at trough and thus deliver tonic BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. LOXO-305 is also a highly selective molecule, with more than 300-fold more selectivity for BTK versus 370 other kinases tested and no significant inhibition of non-kinase off-targets at 1 μM, thus limiting the potential for off-target mediated toxicities. Collectively, these unique properties of LOXO-305 are expected to deliver more potent, continuous, and selective inhibition of BTK in a variety of settings, potentially resulting in increased efficacy. Of note, the activity of LOXO-305 in diverse preclinical model systems supports this underlying hypothesis.[2]

LOXO-305 is a small molecule that was designed to block the adenosine triphosphate binding site of the BTK competitively, with no evidence of irreversible binding.

1.2. Nonclinical Pharmacokinetics and Toxicology

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

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

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

LOXO-305 was metabolized slowly by human microsomal fractions and hepatocytes. The low rates of metabolism in both these human in vitro systems suggest that LOXO-305 will

have low clearance in humans. In vitro data with cloned expressed cytochrome P450 (CYP) enzymes and human liver microsomes indicate that CYP3A4 is the primary CYP enzyme that metabolizes LOXO-305. It is also a substrate for direct glucuronidation.

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

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

In a Good Laboratory Practice (GLP) in vitro assay for human ether-à-go-go-related gene (hERG) activity, the concentration resulting in 50% inhibition for the inhibitory effects of LOXO-305 on hERG potassium currents was CCI µM, which is approximately CCI higher than the maximum unbound concentration of LOXO-305 in patients treated with the dose of 200 mg QD. There were no LOXO-305-related changes in any cardiovascular endpoints including QTc at single doses up to 60 mg/kg in the GLP cardiovascular study in the conscious telemetry-instrumented dog. The maximum observed plasma concentration (C_{max}) for this dose was CCI ng/mL, which is approximately CCI above the predicted C_{max} (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 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. Additionally, in dogs treated for 15 weeks, two 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 to 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]

Doses evaluated in the 28-day dog study demonstrated a steep dose-response curve for toxicity and pronounced changes in hematologic parameters at high exposures.

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

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

1.3. Potential for Drug-drug Interactions

LOXO-305 showed no detectable inhibition (50% inhibitory concentration [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 1B1 (OATP1B1), organic anion transporting polypeptide 1B3 (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 09 April 2020, safety data were available from 172 treated patients, with 300 mg QD as the highest dose administered (Section 1.4.1). As of 30 March 2020 (data cutoff date), PK data were available from 107 patients (Section 1.4.2).

LOXO-305 was recently investigated in 1 study in healthy volunteers (LOXO-BTK-20014). LOXO-BTK-20014 is a pilot food-effect cross-over study evaluating the effects of food and a proton-pump inhibitor (omeprazole) on the PK of LOXO-305 where 10 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days, each followed by a washout period. 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 single ascending dose 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.

1.4.1. Safety

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

Overall, TEAEs were reported in 123 of 172 treated patients in the safety population and were mild or moderate severity (Grade 1 or 2) in 89 of 123 (51.7%) patients and were Grade 3 or 4 in severity in 33 of 123 (19.2%) patients. The most frequently reported TEAEs occurring in ≥ 10% of patients were fatigue (12.8% total, 7.0% related) and diarrhea (10.5% total, 6.4% related). The most frequently reported drug-related TEAEs (those in > 5% of patients) were fatigue (7.0%), diarrhea (6.4%), and contusion (5.2%). All other drug-related TEAEs occurred in < 5% of patients each. The most frequently reported Grade ≥ 3 TEAEs included neutropenia (4.1% total; 2.9% related), neutrophil count decreased (2.3% total; 1.2%

related), anemia (1.7% total; 0.6% related), fatigue, leukocytosis, and platelet count decreased (each 1.2% total; each 0.6% related), and hypokalemia (1.2% total; none related).

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

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

From AE data reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20014 study, all TEAEs (headache, nausea, and vomiting) were Grade 1 in severity and considered related to LOXO-305. All 3 events were reported by 1 subject and resolved 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 End of Treatment (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).

To date, there have been no clinically significant abnormal findings in vital signs and ECG data in the studies investigating LOXO-305 conducted in healthy volunteers.

1.4.2. Pharmacokinetics

As of 30 March 2020, PK data were available from 107 patients enrolled in LOXO-BTK-18001. Steady-state PK parameters of LOXO-305 in these cancer patients could be derived from data collected on Cycle 1 Day 8 and are shown in Table 1. These data show that LOXO-305 is absorbed after oral administration with a median time to maximum observed plasma concentration (t_{max}) of approximately 2 hours and low clearance (Table 1). Due to the limited sampling interval (0-8 hours), imputation for the 24-hour sample was made from the Cycle 1, Day 8 predose sample, leading to an estimated plasma half-life of approximately 20 hours. Following administration of doses of 100 mg QD higher, mean trough plasma levels of LOXO-305 exceeded the CCI of BTK in vitro (Figure 1).

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

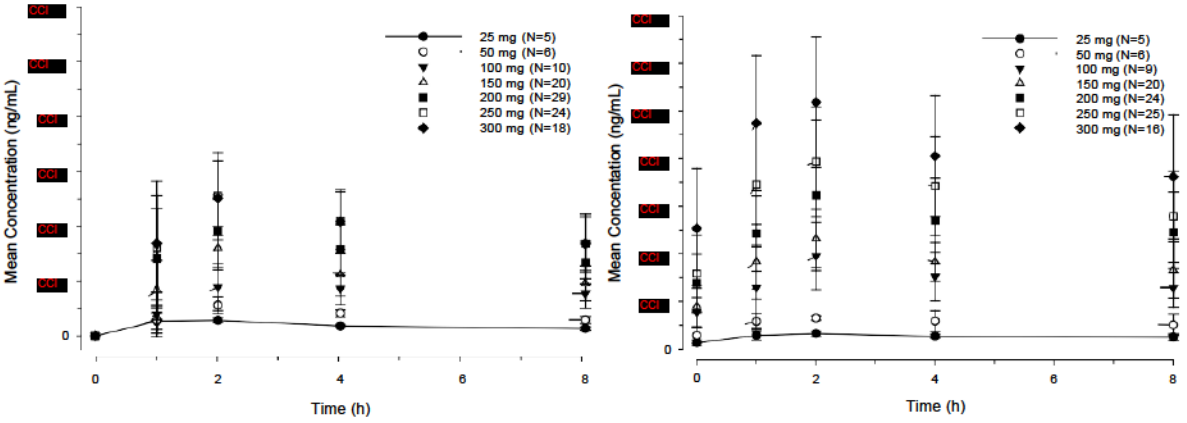
Dose Level	N	C_{max} (ng/mL) Geo mean (%CV)	t_{max} (h) Median (min, max)	AUC_{0-24} (ng*h/mL) Geo mean (%CV)	CL/F (L/h) Geo mean (%CV)	$T_{1/2}$ (h) Geo mean (%CV)
25 mg QD	CCI					
50 mg QD						
100 mg QD						
150 mg QD						
200 mg QD						
250 mg QD						
300 mg QD						

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

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

Data cutoff date: March 30, 2020.

CCI



Data cutoff date: March 30, 2020.

Single doses of 200 mg LOXO-305 were investigated in a study in healthy volunteers (LOXO-BTK-20014, Pilot Food Effect study) in which the PK was determined. Following a

single dose of 200 mg LOXO-305 to patients or healthy subjects, AUC from 0 to 8 hours was similar between the two groups and C_{max} was approximately CCI higher in healthy subjects, as shown in the table below (data on file at the time of protocol development).

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

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

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

In healthy volunteers, the geometric mean single-dose C_{max} of approximately 5450 ng/mL following a 200-mg single dose is CCI below the NOEL (in rat, CCI) for micronuclei induction.

1.5. Study Rationale

Liver disease can cause alterations in drug disposition and PK. Such alterations can reduce the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect plasma protein binding, which in turn could influence the processes of absorption, distribution, and elimination. Results from this study will provide information on the safety, tolerability, and exposure of LOXO-305 in participants with hepatic impairment and participants with normal hepatic function.

This study is being conducted to provide information to develop dosing recommendations for LOXO-305 in subjects with hepatic impairment. The current study will be carried out in subjects with hepatic impairment according to 3 different Child-Pugh (CP) categories[9,10] (mild, moderate, and severe impairment) and also in matched-control healthy subjects. Of these hepatic impairment subjects enrolled per CP category, enrollment will also aim to have at least 4 subjects meet severe hepatic impairment criteria per National Cancer Institute's Organ Dysfunction Working Group (NCI-ODWG) classification, at least 4 subjects meet moderate hepatic impairment criteria per NCI-ODWG classification, and at least 4 subjects meet mild hepatic impairment criteria per NCI-ODWG classification. [11]

There are several methods used to categorize the severity of hepatic impairment. Despite its imperfections, the CP classification is the most widely used and is an acceptable method supported by regulatory agencies (including the United States Food and Drug Administration [FDA] and the European Medicines Agency [EMA]). Further data analysis will be performed using NCI-ODWG classification for hepatic dysfunction (see Section 8).[11] The FDA and EMA Guidelines recommend that the "number of subjects enrolled should be sufficient to detect clinically relevant PK differences." In the current study, up to 8 subjects with mild

hepatic impairment, up to 8 subjects with moderate hepatic impairment, up to 8 subjects with severe hepatic impairment, and 8 to 24 healthy subjects with normal hepatic function will be enrolled. The PK and safety profiles between each hepatic impairment group and their matching (age, sex, and body mass index [BMI]) healthy subjects will be compared.

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 single ascending dose 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 electrocardiogram (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 hepatic 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 hepatic 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}
- 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} ($\%AUC_{extrap}$)
- 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 fraction unbound (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 mild, moderate, or severe impaired hepatic function and healthy subjects with normal hepatic function. Hepatic function will be classified based on the CP classification of hepatic impairment (Table 3).[9,10]

Subjects will be recruited in this study so that up to 24 subjects with hepatic impairment (up to 8 subjects with mild impairment, up to 8 subjects with moderate impairment, and up to 8 subjects with severe impairment, per CP classification – assessed at Screening and verified at Check-in [Day -1]) and 8 to 24 subjects with normal hepatic function are enrolled, with the goal of having at least 6 subjects from each hepatic impairment group per CP classification and at least 6 subjects with normal hepatic function complete the study. Hepatically impaired subjects will be assigned to groups according to CP scores at Check-in (Day -1) to ensure stability of hepatic impairment and subject safety, as determined by the Investigator [or designee]. Subjects will be enrolled within the following groups based on their CP score at Screening and Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 1: Matched-control healthy subjects with normal hepatic function;
- Group 2: Subjects with mild hepatic impairment (CP Class A, score of 5 or 6);
- Group 3: Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9);
- Group 4: Subjects with severe hepatic impairment (CP Class C, score of 10 to 15).

A parallel-design strategy will be adopted for the hepatic impairment groups, with interim reviews (as detailed in Section 8.2) of the safety data after the first 2 subjects from Group 2 (mild hepatic impairment subjects) and Group 3 (moderate hepatic impairment subjects) and matched-control healthy subjects are enrolled and have completed all study-related assessments including the follow-up phone call.

Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), BMI (± 20%), and sex to the completed hepatic impairment subject(s). Should another hepatic 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 hepatic impairment group. Each subject with normal hepatic function may be matched with up to 1 subject within each hepatic impairment group.

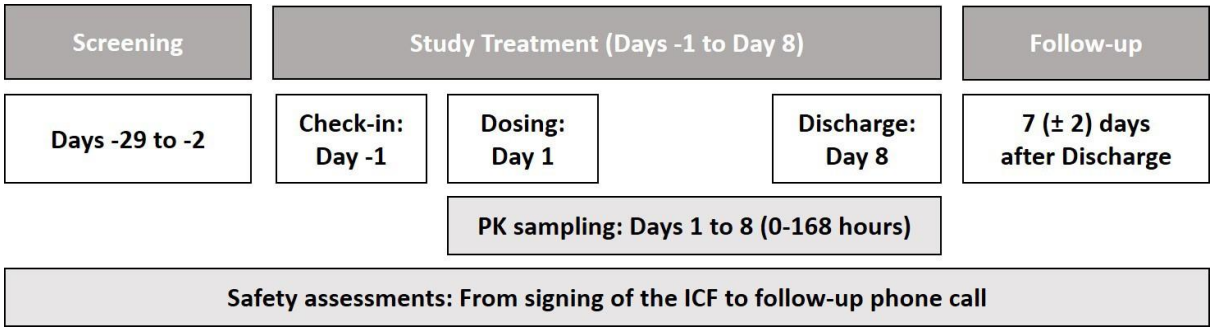
The schematic of the study design is displayed in Figure 2.The start of the study is defined as the date the first subject who is enrolled in the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned a dose of study drug; this definition 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 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. 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 approximately 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 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. For instructions regarding food and water intake, refer to Section 6.2. Pharmacokinetic samples will be obtained through 168 hours postdose.

Figure 2: 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 serious AEs (SAEs) will be collected beginning at informed consent. Adverse events will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship

to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

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

3.2. Child-Pugh Classification

Per FDA Guidance[12] hepatic impairment will be classified as mild, moderate, or severe using the CP System (Table 3),[9,10] and the parameters to determine the CP class for each subject with hepatic impairment will be collected at Screening and Check-in (Day -1). Further data analysis will be performed using NCI-ODWG classification (see Section 8).

Table 3: Child-Pugh Assessment of Hepatic Function

	Points Scored for Observed Findings		
	1	**2**	**3**
Hepatic encephalopathy grade[a]	0	1 or 2[c]	3 or 4[c]
Ascites[b]	Absent	Slight	Moderate
Serum bilirubin, mg/dL (µmol/L)	< 2 (< 34)	2 to 3 (34 to 50)	> 3 (> 50)
Serum albumin, g/dL (g/L)	> 3.5 (> 35)	2.8 to 3.5 (28 to 35)	< 2.8 (< 28)
International normalized ratio	< 1.7	1.7 to 2.3	> 2.3

Chronic Hepatic Impairment is classified into Child-Pugh (CP) class A to C, employing the added score of the 5 parameters in the table above.
Mild Impairment (CP-A): 5 or 6 points; Moderate Impairment (CP-B): 7 to 9 points; Severe Impairment (CP-C): 10 to 15 points.

[a] In this study, hepatic encephalopathy is graded according to the following criteria:

- Grade 0: normal consciousness, personality, neurological examination, or normal electroencephalogram;
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second waves;
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves;
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves;
- Grade 4: unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cycles per second delta activity.

[b] Ascites is graded according to the following criteria:

- Absent: No ascites is detectable by manual examination or by ultrasound investigation, if ultrasound investigation is performed;
- Slight: Ascites palpitation doubtful, but ascites measurable by ultrasound investigation, if performed;
- Moderate: Ascites detectable by palpitation and by ultrasound investigation, if performed;
- Severe: Necessity of paracentesis; does not respond to medication treatment.

[c] A subject with hepatic encephalopathy of Grade 2 or above would not be admitted into the study.

3.3. NCI-ODWG Classification

Subjects will also be classified according to NCI-ODWG criteria (Table 4).[11] Of these hepatic impairment subjects enrolled per CP classification, enrollment will also aim to have at least 4 subjects meet severe hepatic impairment criteria per NCI-ODWG classification, at least 4 subjects meet moderate hepatic impairment criteria per NCI-ODWG classification, and at least 4 subjects meet mild hepatic impairment criteria per NCI-ODWG classification.

Table 4: National Cancer Institute-Organ Dysfunction Working Group for Hepatic Dysfunction Criteria

	NCI-ODWG Criteria	
Hepatic Impairment	**Total Bilirubin**	**AST**
Normal	≤ULN	≤ULN
Mild	> ULN to 1.5 x ULN	>ULN
Moderate	>1.5 to 3 x ULN	Any
Severe	> 3 – 10 x ULN	Any

Abbreviations: AST = aspartate aminotransferase; NCI-ODWG = National Cancer Institute-Organ Dysfunction Working Group; ULN = upper limit of normal.

3.4. Discussion of Study Design

A single-dose, parallel design is the standard design to investigate the PK of a drug in subjects with hepatic impairment. A parallel design is required to include subjects with hepatic impairment and matched-control healthy subjects with normal hepatic function. A single dose level of 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 hepatic function will be enrolled in this study to serve as a reference group for interpretation of the results. Patients with a range of hepatic impairment will be included to enhance the ability to detect and characterize the effects of hepatic function on the PK of LOXO-305. 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.

Preclinical and clinical data suggest that LOXO-305 is likely to be well tolerated in healthy human subjects. However, liver disease can cause alterations in drug disposition, reducing the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect plasma protein binding, which in turn could influence the processes of distribution and elimination. Therefore, in this study, a cautious approach will be adopted, where the first 2 subjects from Group 2 (mild hepatic impairment subjects) and Group 3 (moderate hepatic impairment subjects) and matched-control healthy subjects may be dosed concurrently, followed by an interim review of the safety and PK data (if available) before dosing is resumed for the remaining subjects in any (all) group(s) (see Section 8.2).

3.5. 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

Up to 8 subjects will be enrolled into each hepatic impairment treatment group to have at least 6 subjects from each group complete the study. Up to 24 subjects will be enrolled into the matched-control healthy subject group to have at least 6 healthy subjects matched to each hepatic impairment treatment group complete the study. Healthy control subjects will be matched demographically to hepatically 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. Child-Pugh class score (subjects with hepatic impairment only)
4. NCI-ODWG class score (subjects with hepatic impairment only)
5. Demographic data
6. Medical history (including review of medication[s])
7. Height, weight, and BMI
8. Complete physical examination (Section 7.2.5)
9. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
10. 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)
11. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
12. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
13. Screens for hepatitis C virus (HCV) antibody (healthy matched-control subjects only), 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 equivalent (Appendix 2)
14. Hemoglobin A1c (HbA1c) test (Appendix 2)
15. Screen for selected drugs of abuse, including cotinine (healthy matched-control subjects only) and alcohol (breath or urine test [Appendix 2])
16. Estimated glomerular filtration rate (eGFR; Appendix 2)
17. Serum pregnancy test (for female subjects only; Appendix 2)
18. Follicle-stimulating hormone (FSH) test (for post-menopausal female subjects only; Appendix 2)

19. 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. Child-Pugh class score (subjects with hepatic impairment only)
3. NCI-ODWG class score (subjects with hepatic impairment only)
4. Interim medical history, including concomitant medication(s)
5. Weight and BMI
6. Abbreviated 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 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. Screen for COVID-19 via PCR or equivalent (Appendix 2)
12. Screen for selected drugs of abuse, including cotinine (healthy matched-control subjects only) and alcohol (breath or urine test [Appendix 2])
13. eGFR (Appendix 2)
14. Serum pregnancy test (for female subjects only; Appendix 2)
15. 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.

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 hepatic 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 levels consistent with post-menopausal status per the laboratory's reference ranges. All female subjects must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin; serum quantitative human chorionic gonadotropin tests may be used for confirmation as needed) at Screening and Check-in (Day -1). Female subjects are required to refrain from donation of ova from Check-in (Day -1) until 6 months after Day 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 hepatic impairment in sex, age (± 10 years), and BMI (± 20%). Note: Each matched-control healthy subject may be matched with up to 1 subject within each hepatic impairment group.

Additional inclusion criteria for subjects with hepatic impairment

9. Considered to have mild, moderate, or severe hepatic impairment (of any etiology) that has been clinically stable (no acute episodes of illness due to deterioration in hepatic 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 hepatic impairment, subjects must have a CP score of 5 to 6 (mild), 7 to 9 (moderate), or 10 to 15 (severe), with known medical history of liver disease (with or without a known history of alcohol abuse).
10. Currently on a stable medication regimen, defined as not starting new drug(s) or significantly changing drug dosage(s) within 14 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 Covance Medical Monitor, Investigator (or designee) and Sponsor.
11. Non-hepatic abnormal laboratory values must be not clinically significant, as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor.
12. Anemia secondary to hepatic 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 Covance Medical Monitor, Investigator (or designee), and/or Sponsor:
    a. pancreatitis
    b. peptic ulcer disease
    c. intestinal malabsorption
    d. gastric reduction surgery
    e. 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, 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, hernia repair, and cholecystectomy will be allowed. Bariatric surgery 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 exclusion criteria #23, #24, #25, #26, #36, and #37 below) at Screening or Check-in (Day -1). Rechecks of clinically significant abnormal clinical laboratory results (excluding those further defined in exclusion criteria #23, #24, #25, #26, #36, and #37 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. Clinically significant abnormality, as determined by the Investigator (or designee), from physical examination at Screening and/or Check-in (Day -1).
6. Positive serologic test for HbsAg, HBV IgM core antibody, or HIV antibody at Screening. Subjects who are positive for HBV IgM by antibody will require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HBV PCR positive or for whom a PCR is unable to be obtained will not be eligible.
7. Positive PCR test (or equivalent) for COVID-19 at Screening or Check-in (Day -1). Further details regarding COVID-19 testing (including procedures for subjects who test positive at any time throughout CRU confinement) are specified in a separate document.
8. 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.
9. Consumption of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET.
10. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET.
11. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
12. Participation in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to Day 1.
13. Use or intention to use any prescription or over-the-counter medications (including but not limited to any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers [including herbal products such as St. John's wort], strong P-glycoprotein (P-gp) inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists and drugs that prolong QT/QTc interval, 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 hepatically impaired, needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) and deemed acceptable Medical Monitor, Investigator (or designee), and Sponsor, and provided that the subject has been on a stable dose for a minimum of 14 days prior to Day 1.
14. History of a major surgical procedure within 30 days prior to Screening.
15. 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.
16. Poor peripheral venous access.
17. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
18. Receipt of blood products within 2 months prior to Check-in (Day -1).

19. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

Additional exclusion criteria for matched-control healthy subjects:

20. 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.
21. ECG findings deemed abnormal by the Investigator (or designee) at Screening, Check-in (Day -1), or prior to dosing on Day 1.
22. 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 beats per minute (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.
23. Abnormal liver function tests (LFTs), as defined by aspartate aminotransferase, alanine aminotransferase, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or Check-in (Day -1). Rechecks of LFTs, amylase, and lipase 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.
24. eGFR $\leq$ 90 mL/minute/1.73m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at Screening or Check-in (Day -1). Rechecks of out-of-range eGFR 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 fall within the range stated above.
25. 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.

26. Hemoglobin, below the lower limit of normal range at Screening or Check-in (Day -1). Rechecks of hemoglobin below the lower limit of 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 are stable or normalizing.
27. Known ongoing alcohol and/or drug abuse within 2 years prior to Screening, or evidence of such abuse as indicated by the laboratory assays for drugs of abuse (including cotinine and alcohol) conducted during Screening and/or at Check-in (Day -1). Tests for drugs of abuse (including cotinine and alcohol) must be negative at both Screening and Check-in (Day -1).
28. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET.
29. Significant history or clinical manifestation of any allergic, dermatological, biliary, hepatic, gastrointestinal, renal, metabolic, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), neurological, or psychiatric disorder (as determined by the Investigator [or designee]). Note: subjects with a history of appendectomy and/or hernia repairs will be acceptable.
30. History of diabetes mellitus; HbA1c $\geq$ 6.5%.
31. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).
32. Has completed or withdrawn from any other study investigating LOXO-305 and have previously received the investigational product within the last 30 days.
33. Positive serologic test for HCV antibody at Screening. Subjects who are positive for HCV by antibody will require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HCV PCR positive or for whom a PCR is unable to be obtained will not be eligible.

Additional exclusion criteria for subjects with hepatic impairment:

34. QTcF value of > 450 msec for subjects with mild or moderate hepatic impairment or > 470 msec for subjects with severe hepatic 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.
35. 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. Heart rate < 50 or > 99 bpm
    c. Systolic BP < 90 or > 150 mmHg
    d. Diastolic BP < 40 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 hepatic 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 values fall within the ranges referenced above.

36. eGFR of < 90 mL/minute/1.73m^2 calculated using the CKD-EPI equation at Screening or Check-in (Day -1) for subjects with mild or moderate hepatic impairment or eGFR of < 60 mL/minute/1.73m^2 calculated using the CKD-EPI equation at Screening or Check-in (Day -1) for subjects with severe hepatic impairment. Rechecks of out-of-range eGFR 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 fall within the range stated above.
37. Values outside the normal ranges for creatine kinase, LFTs, amylase, and lipase may be acceptable as consistent with the subject's hepatic condition (if stable for 1 month prior to Screening), and if the Investigator (or designee) and Sponsor feel that the results are not clinically significant (based on age and hepatic impairment status).
38. Known ongoing alcohol and/or drug abuse within 1 month prior to Screening, or evidence of such abuse as indicated by the laboratory assays for drugs of abuse (including alcohol) conducted during Screening and/or at Check-in (Day -1). Tests for drugs of abuse (aside from cotinine) must be negative at both Screening and Check-in (Day -1) unless the positive drug screen is considered to be due to the use of a prescription drug which is approved by the Covance Medical Monitor, Investigator (or designee), and Sponsor.
39. 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.
40. 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), Covance Medical Monitor, and Sponsor.
41. History of cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin).
42. Has a portal systemic shunt.
43. Has required new medication for hepatic encephalopathy within the 6 months prior to Check-in (Day -1).
44. 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 hepatic function (Table 5) 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 CRU and the second set of 3 digits will identify the subject (eg, 001-101).

Subject numbers will be used on all study documentation.

Group 1: Matched-control healthy subjects: 001-100 through 001-199

Group 2: Subjects with mild hepatic impairment: 001-200 through 001-299

Group 3: Subjects with moderate hepatic impairment: 001-300 through 001-399

Group 4: Subjects with severe hepatic impairment: 001-400 through 001-499.

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 5: Subject Group and Number of Subjects

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

[a] Hepatic function determined using the Child-Pugh assessment (Section 3.2).

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 hepatically impaired subjects (age [± 10 years], BMI [± 20%], and sex). An individual matched-control healthy subject may be matched with up to 1 subject within each hepatic impairment group (ie, to a maximum of 3 hepatically 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 6).

Table 6: Study Drugs

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(s).

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

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

5.2. Study Treatment Administration

Subjects will receive 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 for at least 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.

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

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

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

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

5.3. Randomization

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 and over-the-counter medications 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 hepatically impaired, needed to stabilize the subject's underlying medical condition (or concurrent baseline conditions) as described below. This includes but is not limited to: moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers (including herbal products such as St. John's wort), strong P-glycoprotein (P-gp) inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, natural or herbal supplements, and HRT.

For hepatically 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 14 days prior to Day 1. Hepatically 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. Hepatically 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.

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

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of LOXO-305 plasma levels, protein binding, and potential analysis of metabolites 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 and protein binding will be recorded on the eCRF.

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

7.1.2. Analytical Methodology

Concentrations of LOXO-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 unbound fraction 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 measurements, 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) that 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 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 (healthy matched-control subjects only), HbsAg, HBV IgM core antibody, and HIV antibody will be performed at Screening.

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

A urine drug screen for selected drugs of abuse (including cotinine [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 pregnancy test (female subjects only [serum quantitative may be used for confirmation if needed]) and an FSH test (post-menopausal female subjects only) will be performed at the timepoints specified in Appendix 4.

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

7.2.3. Vital Signs

Vital 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.

The physical examination at Screening will include hepatic encephalopathy and ascites evaluations for the CP assessment.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

A total of up to 24 subjects with hepatic impairment (up to 8 subjects from each hepatic impairment group, per CP classification) and approximately 8 to 24 matched-control healthy subjects with normal hepatic function will be enrolled in the study with the goal of having at least 6 subjects from each hepatic impairment group per CP classification and at least 6 subjects with normal hepatic function complete the study. Of these hepatic impairment subjects enrolled per CP category, enrollment will also aim to have at least 4 subjects meet severe hepatic impairment criteria per NCI-ODWG classification, at least 4 subjects meet moderate hepatic impairment criteria per NCI-ODWG classification, and at least 4 subjects meet mild hepatic impairment criteria per NCI-ODWG classification. 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 hepatic function.

8.2. Interim Analysis

Interim reviews of safety data will be conducted after the first 2 subjects from Group 2 (mild hepatic impairment subjects) and Group 3 (moderate hepatic impairment subjects) and matched-control healthy subjects are enrolled and have completed all study-related assessments including the follow-up phone call. The safety data will include AEs and SAEs, vital signs, physical examinations, ECGs, and clinical laboratory evaluations. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Each interim review will be a teleconference between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor to discuss safety data.

If available, PK data and matched-control healthy subject data may also be used during the interim review.

8.3. Analysis Populations

8.3.1. Study 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 time to maximum concentration. The impact of protocol deviations on 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}	area under the concentration-time curve (AUC) from hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
AUC_{0-inf}	AUC from 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
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 (ln)(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

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

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
$AUC_{0-inf,u}$	Unbound AUC_{0-inf}, calculated as AUC_{0-inf}*f_u
$CL/F_{,u}$	Unbound CL/F, calculated as Dose/$AUC_{0-inf,u}$
$V_z/F_{,u}$	Unbound V_d/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 analysis 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 separately by CP and NCI-ODWG hepatic 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 protein binding will be tabulated separately by CP and NCI-ODWG hepatic function group.

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 mild, moderate, or severe hepatic impairment, compared to subjects with normal hepatic function. To evaluate the effect of hepatic function group on the PK of a single dose of LOXO-305, paired t-tests will be performed for each hepatic impairment group (by CP classification) versus the normal group with respect to 1-to-1 matching.

In addition, an analysis of covariance (ANCOVA) will be performed on the natural log (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 hepatic impairment (severe, moderate, and mild by CP classification) and healthy matched-control subjects, a categorical covariate (sex), and continuous covariates (age and BMI). Ratios of least squares means and 90% confidence intervals (CIs) will be calculated using the exponentiation of the difference between hepatic 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 natural log (ln)-transformed unbound $AUC_{0\text{-}t}$, unbound $AUC_{0\text{-}inf}$, and unbound C_{max}. The specific procedures will be documented in the SAP. Similar ANCOVA analysis will be applied for evaluating the effect of hepatic function group by NCI-ODWG classification.

8.5. Safety Analysis

All safety assessments, including AEs and 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 hepatic function 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 22.1 (or higher). The incidence of AEs for each hepatic function (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 hepatic function.

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 client-provided specifications. The final datasets structure will be verified using Web Submission Data Manager®, while the dataset content will be peer reviewed by an independent programmer.

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

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

8.7. Quality Control and Quality Assurance

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

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

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

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

9.2. Site Initiation Visit/Investigator Meeting

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

9.3. Disclosure

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

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

9.4. Monitoring

Covance (on behalf of the Sponsor) will designate Study Monitors who will be responsible for monitoring this clinical trial. Covance's Study Monitors 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), Applications for FDA Approval to Market a New Drug (21 CFR 314), and Radioactive Drugs for Certain Research Uses (21 CFR 361.1), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable International Council for Harmonisation (ICH) Guidelines, are commonly known as Good Clinical Practices, 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

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11. APPENDICES

Appendix 1: Adverse Event Reporting

Adverse Events

Definition of Adverse Events

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

The following are all AEs:

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

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

Categorization of Adverse Events

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

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

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

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

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

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

Pregnancy

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed through End of Study (EOS) or Early Termination (ET; if the subject discontinues from the study and does not complete a follow-up phone call) and for up to 90 days after 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; ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator (or designee) should follow the procedures for reporting an SAE.

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

All pregnancies should be recorded on the AE electronic Case Report Form (eCRF; as appropriate), in addition to completion of the required pregnancy forms. If the Investigator (or designee) suspects that a pregnancy was the result of an interaction between the study

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

Definition of Serious Adverse Events

An SAE (by Food and Drug Administration [FDA] definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

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

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

Unexpected Adverse Drug Reaction

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

Reporting

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

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

email: SAEIntake@Covance.com

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

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

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

Appendix 2: Clinical Laboratory Evaluations

<table>
<tr>
<th>Clinical Chemistry Panel (Fasted):</th>
<th>Hematology Panel:</th>
<th>Other Tests:</th>
</tr>
<tr>
<td rowspan="2">Alanine aminotransferase
Albumin
Alkaline phosphatase
Amylase
Aspartate aminotransferase
Bilirubin (direct and total)
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatine kinase
Creatinine
Glucose
Iron
Lipase
Magnesium
Phosphorus
Potassium
Sodium
Total protein
Triglycerides
Uric acid</td>
<td rowspan="2">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[a,d]
SARS-CoV-2 (COVID-19) test</td>
</tr>
<tr>
<td>Coagulation Parameters:</td>
</tr>
<tr>
<td rowspan="2">Partial thromboplastin time
Prothrombin time
International normalized ratio</td>
<td rowspan="2">Urinalysis:</td>
<td>Serology:[b]</td>
</tr>
<tr>
<td rowspan="2">Human immunodeficiency virus antibody
Hepatitis B surface antigen
Hepatitis B virus immunoglobulin M core antibody[f]
Hepatitis C virus antibody (healthy matched-control subjects only)[f]</td>
</tr>
<tr>
<td>Urine Drug Screen:[a]</td>
<td rowspan="2">Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic examination including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)</td>
<td>For Female Subjects only:</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>
<td>Pregnancy test (serum qualitative, serum quantitative may be used for confirmation if needed)[c]
Follicle-stimulating hormone (post-menopausal female subjects only)[b]</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. Subjects who are positive for hepatitis B virus (HBV) immunoglobulin M or hepatitis C virus (HCV) by antibody will require confirmation by polymerase chain reaction (PCR) before enrollment to detect presence of active virus. Subjects who are HBV or HCV PCR positive or for whom a PCR is unable to be obtained will not be eligible.

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	5	20
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:	**157 mL**

[a] Estimated glomerular filtration rate will be assessed as part of the clinical chemistry sample.

Note: Although the total maximum volume to be analyzed is anticipated to be approximately 157 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[u]	Follow-up Phone Call (EOS)
			Day 1	Days 2 to 7	Day 8	7 (± 2) days post EOT or ET[w]
Confined to the CRU		X	X	X	X	
Inclusion/Exclusion Criteria	X	X				
Informed Consent	X					
Demographics	X					
CP Class Score[b]	X	X				
NCI-ODWG Class Score[b]	X	X				
Medical History	X	X[c]				
Height/Weight/BMI	X[d]	X[d]				
Physical Examination[e]	X	X			X	
12-Lead ECG[f]	X	X	X		X	
Vital Signs[g]	X[h,i]	X[h,i]	X[i]	X	X[h,i]	
HDYF? Inquiry[j]	X	X	X	X	X	X
AEs/SAEs[k]	X	X	X	X	X	X
LOXO-305 Dose[l]			X			
CCI						
Clinical Laboratory Evaluations[o]	X	X		X[v]	X[v]	
COVID-19 Test[p]	X	X				
eGFR	X	X				
Hepatitis and HIV Screen	X					
HbA1c Test	X					
Drug Screen[q]	X	X				
Prior and Concomitant Medications[r]	X	X	X	X	X	X
Serum Pregnancy Test[s]	X	X		X[v]	X[v]	
FSH Test[t]	X					
TSH Test	X					

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; COVID-19 = SARS-CoV-2; CP=Child-Pugh; 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; NCI-ODWG = National Cancer Institute – Organ Dysfunction Working Group; PK = pharmacokinetic; SAE = serious adverse event; TSH = Thyroid Stimulating Hormone; UA = urinalysis.

a. For details on study procedures, see Section 7.
b. Subjects with hepatic impairment only. Child-Pugh and NCI-ODWG scores will be calculated at Screening and Check-in (Day -1); hepatically impaired subjects will be assigned to groups according to CP scores at Check-in (Day -1) to ensure stability of hepatic impairment and subject safety, as determined by the Investigator (or designee).
c. Interim medical history only.

d. Height collected at Screening only, body mass index based on Screening height.
e. 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).
f. 12-lead ECGs will be obtained at Screening, Check-in, Day 1 (predose and 2 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.
g. Vital sign measurements (supine BP and pulse rate) will be obtained at Screening and Check-in (Day 1), Day 1 (predose and 2 hours postdose), 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. BP and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes. 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.
h. Body temperature and respiratory rate will be obtained at Screening, Day -1, and at EOT (Day 8) or ET.
i. Oxygen saturation measured by pulse oximetry will be measured at Screening, 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.
j. An 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.
k. 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.
l. 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 at least 2 hours postdose.

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o. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and urinalysis (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.
p. 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 equivalent.
q. 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.
r. 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 hepatic 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.
s. Female subjects only.
t. Post-menopausal female subjects only.

u. 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 serum pregnancy test results (female subjects only) are to be available for review by the Investigator (or designee) prior to subject release from the CRU at the EOT visit and prior to subject release from the CRU at the ET visit if available.
v. Clinical laboratory evaluations and serum 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 serum pregnancy test (female subjects only) will be performed on the day of subject release from the CRU if the subject terminates early (ET).
w. 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 7th October 2020) incorporated the following changes in Protocol Version 1.0 (dated 7th August 2020):

- Additional data from non-clinical studies with LOXO-305 has been added to Section 1.2, *Nonclinical Pharmacokinetics and Toxicology*.
- Additional data from clinical studies with LOXO-305 has been added to Section 1.4, *Summary of Clinical Experience*, Section 1.4.1, *Safety*, and Section 1.6, *Risk Assessment.*
- The Protocol has been updated to allow glucose tablets to be administered as needed for treatment of hypoglycaemia during the study as a safety precaution.
- The number of subjects aimed to be enrolled into each National Cancer Institute's Organ Dysfunction Working Group (NCI-ODWG) classification for hepatic impairment has been clarified throughout the Protocol from a minimum of 4 subjects with mild and moderate hepatic impairment by NCI-ODWG classification, to at least 4 subjects meeting moderate hepatic impairment criteria per NCI-ODWG classification, and at least 4 subjects meeting mild hepatic impairment criteria per NCI-ODWG classification.
- Table 4, *National Cancer Institute-Organ Dysfunction Working Group for Hepatic Dysfunction Criteria* has been corrected such that the criteria for mild hepatic impairment and severe hepatic impairment are consistent with the criteria used in the publication cited in the Protocol.
- The requirements for hepatitis C virus antibody testing have been clarified throughout the Protocol to state that this will be conducted in healthy matched-control subjects only to be consistent with Section 4.1, *Screening Procedures*, #13.
- The requirements for hepatitis B virus testing have been clarified throughout the Protocol to state that it will be performed using an immunoglobulin M (IgM) core antibody test.
- The requirements for oral temperature measurements to be taken have been revised throughout the Protocol, to allow any type of temperature measurements to be taken to provide flexibility to study sites.
- The duration of contraceptive requirements for male subjects without documentation of sterilization has been clarified to state that male subjects must follow 1 of the contraception methods listed under inclusion criterion #5b from Day 1 through 6 months after Day 1.
- The contraceptive requirements for sexual intercourse between male subjects with female partners who are pregnant or breastfeeding has been clarified to state that this should be avoided from Check-in (Day -1) through 6 months after Day 1, unless the male subject uses a condom with spermicide.
- Inclusion criterion #12 has been amended to reduce the acceptable hemoglobin level from ≥ 9 g/dL to ≥ 8 g/dL for subjects who have anemia secondary to hepatic disease, where anemia symptoms are not clinically significant. This criterion has been updated

to more accurately reflect the range typically seen in a hepatic impairment population, without impacting subject safety.

- Exclusion criterion #4 has been revised to allow clinically significant (as determined by the Investigator [or designee]) abnormal clinical laboratory results (excluding those further defined in exclusion criteria #23, #24, #25, #26, #36, and #37) to be repeated 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. This change has been made to account for transient abnormal results.
- Exclusion criteria #8 and #9 and Section 6.2, *Diet, Fluid, and Activity Control* have been updated to remove the Investigator (or designee) and Sponsor discretion for inclusion of subjects who consume grapefruit/grapefruit juice, Seville oranges or its juice or alcohol or caffeine-containing foods or beverages within the specified time prior to Check-in (Day -1). This has been amended as consumption of any of the noted items in the specified time prior to Check-in (Day -1) would not be permitted in any circumstance.
- Exclusion criterion #13 and Section 6.1, *Concomitant Therapies* has been updated to include strong P-glycoprotein inhibitors, proton pump inhibitors, antacids, and H_2-receptor antagonists in the list of specified restricted over-the-counter and prescription medications to provide further guidance to the sites.
- The duration of the restriction for prescription and over-the-counter medication prior to Day 1 in Exclusion criterion #13, Section 6.1, *Concomitant Therapies*, and Appendix 4, *Schedule of Assessments***,** footnote *r* has been amended to 14 days **or** 5 half-lives (whichever is longer) prior to Day 1 to account for medications that may have a prolonged half-life.
- Exclusion criterion #16 '*Estimated glomerular filtration rate (eGFR) of <50 mL/min at Screening or Check-in (Day -1) using the Modification of Diet in Renal Disease formula*', has been replaced with exclusion criteria #24 (healthy subjects) and #36 (hepatic impairment subjects only). Exclusion criteria #24 and #36 specify that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will be used to calculate eGFR, and per Food and Drug Administration (FDA) recommendation, healthy subjects with an eGFR $\leq$ 90 mL/minute/1.73m^2 , mild and moderate hepatically impaired subjects with an eGFR of $\leq$ 90 mL/minute/1.73m^2, and severe hepatically impaired subjects with an eGFR of < 60 mL/minute/1.73m^2 at Screening and Check-in (Day -1) will be excluded. Rechecks of out-of-range eGFR 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 fall within the range stated above. Appendix 2, *Clinical Laboratory Evaluations* has been amended to state that the CKD-EPI equation will be used to calculate eGFR.
- The exclusion of subjects for white blood cell count and platelet count below the lower limit of normal range at Screening and Check-in (Day -1) has been removed from exclusion criterion #26. Instead, subjects with clinically significant (as determined by the Investigator [or designee]) abnormal white blood cell count and platelet count (that do not fall within normal ranges or do not stabilize upon repeat assessment) will be excluded per exclusion criterion #4.

- Exclusion criteria #20, #22, #23, #25, #26, #34, and #35 have been updated to allow out of the specified range values that are not clinically significant (as determined by the Investigator [or designee]) to be permitted to be repeated up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 (where applicable) to confirm eligibility for study. This change has been made to account for transient abnormal results.
- Exclusion criterion #32 has been clarified to state the duration of time in which the subject should not have previously received the investigational product is within the last 30 days.
- The limit for QT interval corrected for heart rate using Fridericia's method (QTcF) in exclusion criterion #34 has been revised to > 450 msec for subjects with mild or moderate hepatic impairment or > 470 msec for subjects with severe hepatic impairment at Screening, Check-in (Day -1), or predose on Day 1 per FDA recommendation.
- Exclusion criterion #35 has been updated to clarify that out-of-range vital signs parameters judged as non-clinically significant will be based on hepatic impairment status and subject age.
- Exclusion criterion #37 has been updated to clarify that the decision to deem creatine kinase, liver function tests, amylase, and lipase values clinically significant will be based on hepatic impairment status as well as age.
- Section 4.5, *Subject Number and Identification* has been clarified to include guidance on the numbering of subjects by hepatic function group (the second set of digits).
- Clarification that water will be restricted for 1-hour predose and 1-hour postdose, with the exception of water administered for dose administration has been provided.
- An analysis of covariance statistical analysis has been added to Section 8.4.2, *Statistical Methodology* for natural log (ln)-transformed unbound $AUC_{0\text{-}t}$, unbound $AUC_{0\text{-}inf}$, and unbound C_{max} per FDA recommendation.
- Appendix 4, *Schedule of Assessments***,** footnote *o* has been clarified to specify the measurement timepoint postdose for clinical laboratory evaluations.
- Appendix 4, *Schedule of Assessments***,** footnotes *f*, *g,* and *i,* have been clarified to specify the measurement timepoint postdose and the allowed measurement window for 12-lead electrocardiograms, vital signs, and oxygen saturation.
- 12-lead ECGs are required to be assessed at Screening, Check-in (Day -1), and predose on Day 1 according to exclusion criterion #22 of the Protocol. Appendix 4, *Schedule of Assessments,* erroneously omitted a 12-lead ECG assessment predose on Day 1 and has been revised to include this.

Minor updates:

- The amendment/version number and date were updated throughout the protocol.
- Typographical errors and formatting errors were corrected, and minor clarifications and corrections were made, as necessary.
- The synopsis was updated to be consistent with the changes made to the body text.