Protocol LOXO-BTK-20008

A Phase I, Open Label, Fixed-sequence Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on the Pharmacokinetics of a Single Dose of Intravenous and Oral Midazolam (CYP3A4 Substrate) in Healthy Subjects

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I have read the protocol and approve it:

13-Sep-20 | 23:26:02 PDT

Date

INVESTIGATOR AGREEMENT

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

PPD

11 SEP 2020
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STUDY IDENTIFICATION

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SYNOPSIS

Study Title

A Phase I, Open Label, Fixed-sequence Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on the Pharmacokinetics of a Single Dose of Intravenous and Oral Midazolam (CYP3A4 Substrate) in Healthy Subjects

Objectives

The primary objectives of the study are:

- to assess the effect of multiple oral doses of LOXO-305 on the pharmacokinetics (PK) of a single oral dose of midazolam in healthy subjects
- to assess the effect of multiple oral doses of LOXO-305 on the PK of a single intravenous (IV) dose of midazolam in healthy subjects

The secondary objectives of the study are:

- to assess the safety and tolerability of multiple oral doses of LOXO-305 when administered alone, coadministered with a single oral dose of midazolam and coadministered with a single IV dose of midazolam.
- to assess the PK of single and multiple doses of LOXO-305 when given alone or with midazolam in healthy subjects.

The exploratory objective of the study is:

- to assess the effect of a single oral dose of LOXO-305 and steady state LOXO-305 on the PK of CCI [redacted] as biomarkers of the human organic anion transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) inhibition in healthy subjects.

Study Design

This is a Phase 1, open-label, 2-period, fixed-sequence drug-drug interaction study to investigate the effect of multiple oral doses of LOXO-305 on the PK of a single oral dose of midazolam and on the PK of a single IV dose of midazolam in healthy subjects. The study will also assess the single and multiple oral dose PK of LOXO-305 and the effect of a single oral dose of LOXO-305 and the effect of LOXO-305 at steady state (following multiple dose administration) on the PK of CCI [redacted] III as biomarkers of OATP1B1 and OATP1B3 inhibition in healthy subjects.

In Period 1, Day 1, a single 250 µg (0.25 mL of 1-mg/mL solution) IV bolus dose of midazolam will be administered over approximately 30 seconds in the morning following a 10-hour fast prior to dosing and a 4-hour fast postdose. On Day 3, a single 500 µg (0.25 mL of 2-mg/mL syrup) oral dose of midazolam will be administered in the morning following a fast of at least 10 hours prior to dosing and 4 hours postdose. On Day 3, the oral midazolam dose will be administered alone at the actual time of the Day 1 IV midazolam dose

(± 1 hour). Blood samples for concentration of midazolam and 1-hydroxymidazolam (1-OH-midazolam), and CCI in plasma will be collected on Days 1, 2, 3, and 4 (in accordance with the Schedule of Assessments [Appendix 4]).

In Period 2 (starting on Day 5), oral doses of 200 mg LOXO-305 will be administered once daily (QD) for 13 consecutive days (Days 5 through 17) in the morning. On Days 5, 14, 15, and 17 oral doses of 200 mg LOXO-305 will be administered following a fast of at least 10 hours prior to dosing and at least 4 hours postdose. On Day 6 through 13, and Day 16 oral doses of 200 mg LOXO-305 will be administered following a fast of at least 2 hours prior to dosing and 1-hour postdose, with the exception of days where clinical laboratory evaluations are performed. On Days 5 through 14, and Day 16, 200 mg LOXO-305 will be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour). On the morning of Day 15, an oral dose of 200 mg LOXO-305 will be administered 2 hours (± 15 minutes) prior to administering a single 250 µg (0.25 mL of 1-mg/mL solution) IV bolus dose of midazolam. On the morning of Day 17, an oral dose of 200 mg LOXO-305 will be administered first before a single oral 500 µg (0.25 mL of 2-mg/mL syrup) dose of midazolam is administered (within 5 minutes) in accordance with the Schedule of Assessments [Appendix 4]). On Days 15 and 17, LOXO-305 will be administered at the actual time of the Day 1 IV midazolam dose (± 1 hour). Blood samples for concentration of LOXO-305 and CCI in plasma will be collected on Days 5 through 16 (in accordance with the Schedule of Assessments [Appendix 4]). Blood samples for concentration of midazolam, 1-OH-midazolam, and LOXO-305 in plasma will be collected on Days 15, 16, 17, and 18. Additionally, blood samples for concentration of LOXO-305 in plasma will be collected on Days 19, 20, and 21 (up to 100 hours post-LOXO-305 dose on Day 17; in accordance with the Schedule of Assessments [Appendix 4]).

There will be a washout period of 2 days between the IV dose of midazolam and the oral dose of midazolam on Days 1 and 3 (Period 1) and Days 15 and 17 (Period 2), respectively.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 21 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. A follow-up phone call will occur for all subjects who received at least 1 dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET.

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

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

In this study, physical examinations, 12-lead electrocardiograms (ECGs), vital sign measurements, oxygen saturation measured by continuous pulse oximetry, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, hematology panel, urinalysis (UA; Appendix 2) and recording of concomitant medications will be

performed at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 4).

Adverse events (AEs) and serious 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 Early Termination [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

Sixteen healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. This is a Phase 1 study and the sample size is not based upon any formal power calculations but is consistent with previous studies of a similar design. Sixteen subjects are anticipated to be sufficient to provide a reliable estimate of the magnitude and variability of the interaction.

Every attempt will be made to enroll at least 4 subjects of each sex in the study.

Main Criteria for Inclusion

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

Investigational Medicinal Products, Dose, and Mode of Administration

In Period 1, Day 1, a single IV bolus dose of 250 µg midazolam administered as 0.25 mL of 1-mg/mL solution will be administered in the morning over approximately 30 seconds following a 10-hour fast prior to dosing and a 4-hour fast postdose. On Day 3, a single oral dose of 500 µg midazolam administered as 0.25 mL of 2-mg/mL syrup will be administered in the morning following a 10-hour fast prior to dosing and a 4-hour fast postdose. On Day 3, the oral midazolam dose will be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour).

In Period 2, oral doses of 200 mg LOXO-305 will be administered QD in the morning for 13 consecutive days (Days 5 through 17). On Days 5, 14, 15 and 17, oral doses of 200 mg LOXO-305 will be administered QD in the morning following a fast of at least 10 hours prior to dosing and at least 4 hours postdose. On Days 6 through 13, and Day 16 oral doses of

200 mg LOXO-305 will be administered QD in the morning following a fast of at least 2 hours prior to dosing and 1-hour postdose, with the exception of days where clinical laboratory evaluations are performed. On Days 5 through 14, and Day 16, 200 mg LOXO-305 will be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour). On the morning of Day 15, an oral dose of 200 mg LOXO-305 will be administered 2 hours (± 15 minutes) prior to administering a single 250 µg (0.25 mL of 1-mg/mL solution) IV bolus dose of midazolam. On the morning of Day 17, an oral dose of 200 mg LOXO-305 will be administered first before a single oral 500 µg (0.25 mL of 2-mg/mL syrup) dose of midazolam is administered (within 5 minutes). On Days 15 and 17, LOXO-305 will be administered at the actual time of the Day 1 IV midazolam dose (± 1 hour).

Duration of Subject Participation in the Study:

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

Length of CRU Confinement: Up to 22 days (Days -1 to 21).

Planned Study Conduct Duration: Up to 59 days (Screening through follow-up call).

Criteria for Evaluation:

Pharmacokinetics:

Whenever possible, the following PK parameters will be calculated based on plasma concentrations of midazolam (oral and IV) and metabolite 1-OH-midazolam, as appropriate: area under the concentration-time curve (AUC) from hour 0 to the last measurable concentration (AUC_{0-t}), AUC from time 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 (λz), apparent systemic clearance (oral midazolam; CL/F), total clearance (IV midazolam; CL), apparent plasma terminal elimination half-life ($t_{½}$), apparent volume of distribution (oral midazolam; Vz/F), volume of distribution (IV midazolam; V_z), and volume of distribution at steady state (IV midazolam; V_{ss}).

Wherever possible, the following PK parameters will be calculated based on the plasma concentrations of LOXO-305: AUC_{0-t}, AUC during a dosing interval (AUC_{tau}), apparent systemic plasma clearance at steady state ($CL_{,ss}/F$), C_{max}, concentration observed at the end of the dosing interval (C_{trough}), t_{max}, and accumulation ratio (R_{AUC}).

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of CCI following single dose midazolam (IV administration), single dose LOXO-305, and steady-state LOXO-305 (as appropriate): C_{max}, t_{max}, AUC from hour 0 to 24 hours (AUC_{0-24}), and steady state concentration (C_{ss}).

Safety:

Safety will be monitored with AE inquiries, clinical laboratory evaluations, vital sign measurements, ECGs, oxygen saturation measured by pulse oximetry, and physical examinations.

Statistical Methods

The primary analysis planned for this study is a mixed effect model that includes treatment as a fixed effect and subject as a random effect. The analysis will be performed on the ln-transformed midazolam and 1-OH-midazolam PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) and include calculation of least squared (LS) means and the difference between treatment LS means, as well as their corresponding 90% confidence intervals (CIs). The geometric mean ratios and their 90% CIs for each treatment comparison will be constructed using the exponentiation of the difference between LS means and the CIs from the mixed effect model. The ratio of midazolam to 1-OH-midazolam will be summarized.

The same method and model as above will be used to analyze the AUC_{0-24} and C_{max} of CCI parameters.

A steady state analysis will be performed on the ln-transformed C_{trough} concentrations for LOXO-305 using Helmert contrasts.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve from time 0 extrapolated to infinity
1-OH-midazolam	1-hydroxymidazolam
ADL	Activities of Daily Living
AE	adverse event
AUC_{0-24}	area under the concentration-time curve from hour 0 to 24 hours postdose
AUC_{0-inf}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
AUC_{tau}	area under the concentration-time curve during a dosing interval
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BP	blood pressure
BSEP	bile salt exporter pump
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CI	confidence interval(s)
CL	total clearance
CL/F	apparent systemic clearance
$CL_{,ss}/F$	apparent systemic clearance at steady state
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
COVID-19	SARS-CoV-2
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
C_{ss}	steady state concentration
C_{trough}	concentration observed at the end of the dosing interval
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction(s)
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

hERG	human ether-à-go-go-related gene
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDYF?	How Do You Feel?
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LFT	liver function test(s)
ln	natural log
LS	least squares
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OCT	organic cation transporter
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
R_{AUC}	accumulation ratio
RBC	red blood cell(s)
SAE	serious adverse event(s)
SAP	Statistical Analysis Plan
SDD	spray-dried dispersion
SLL	small lymphocytic lymphoma
SOC	system organ class

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_{ss}	volume of distribution at steady state
V_z	volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell(s)
WHO	World Health Organization
λz	apparent terminal elimination rate constant

1. INTRODUCTION

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

1.1. Background

LOXO-305 (also known as LY3527727) is a selective inhibitor of the Bruton's tyrosine kinase (BTK) being developed by Loxo Oncology. 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-305are 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

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

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

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

Targets of toxicity were characterized in repeated dose studies conducted in 2 relevant toxicity species. Certain targets (the hematopoietic and lymphoid systems) were found in both the rat and the dog. Rat specific changes in the pancreas are species specific and seen with other BTK inhibitors. Dog specific changes in lung and large intestine were lesions contributing to moribundity in high dose animals in the 28-day study. Doses evaluated in

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

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

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

1.3. Potential for Drug-drug Interactions

LOXO-305 showed no detectable inhibition (50% inhibitory concentration [IC_{50}] CCI) 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 amendment development, 3 healthy volunteers were given one dose of 200 mg of LOXO-305, 12 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days (1 of which was co-administered with itraconazole), each followed by a washout period, and 3 healthy volunteers were given 200 mg of LOXO-305 on 3 separate days (1 of which was 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, and up to 900 mg doses, where, at the time of protocol amendment development 6 healthy volunteers were given a single dose of 300 mg of 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 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 amendment development). From preliminary AE data reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20006 study, all TEAEs (belching, bloating, insect bite, aphthous ulcer, muscle twitch) were Grade 1 in severity and bloating was considered related to LOXO-305. All TEAEs were reported by 3 subjects and resolved prior to End of Treatment (EOT; data on file at the time of protocol amendment development). There were no AEs reported following LOXO-305 administration in 6 healthy volunteers in the LOXO-BTK-20017 study from preliminary data available (data on file at the time of protocol amendment development).

1.4.2. Pharmacokinetics

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

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

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

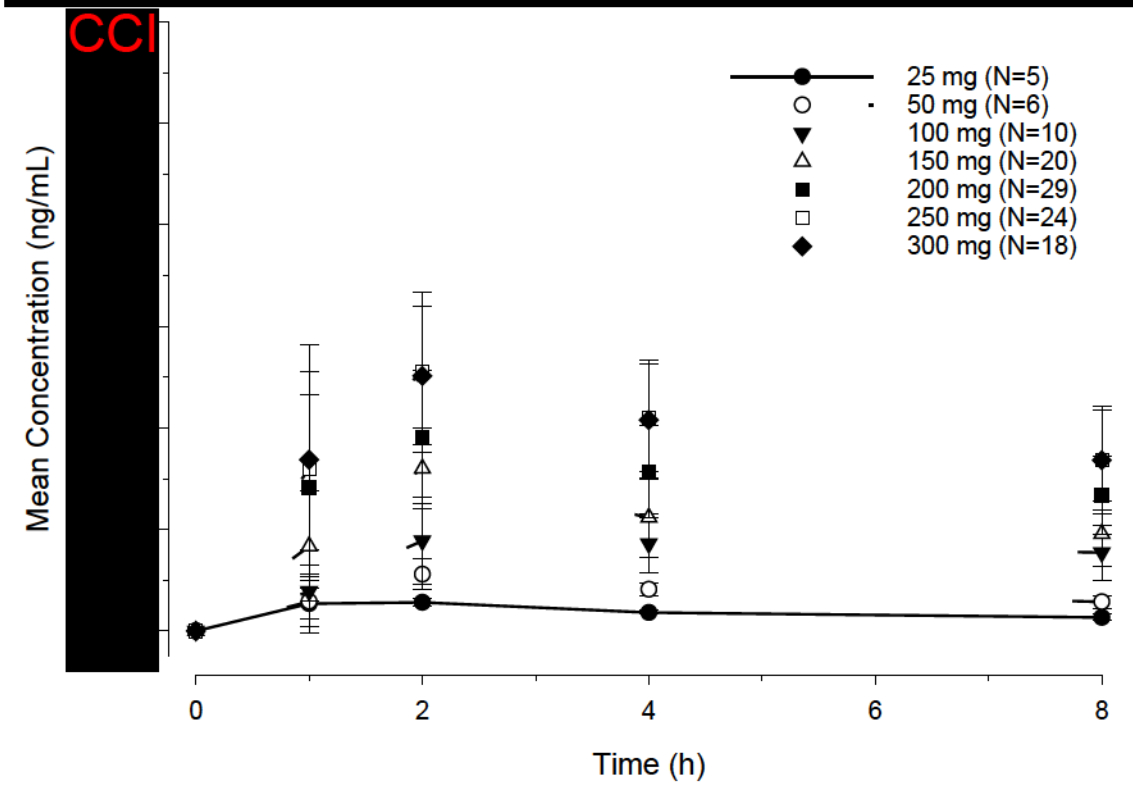
250 mg QD	CCI
300 mg QD	

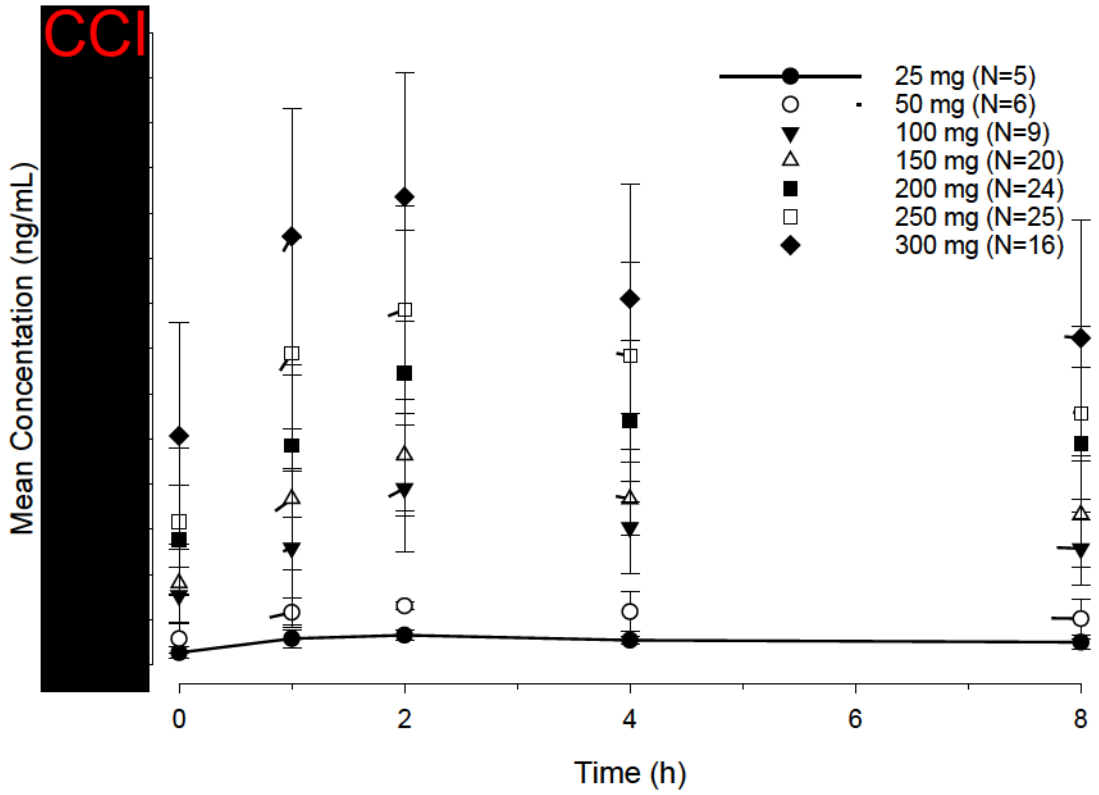
Abbreviations: AUC_{0-24} = area under the concentration-time curve from time 0 to 24 hours; CL/F = apparent oral clearance; C_{max} = maximum drug concentration, Geo mean = Geometrical mean, N = number of subjects; PK = pharmacokinetic; QD = once daily; %CV = coefficient of variation in percent; $T_{1/2}$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

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

Data cutoff date: March 30, 2020.

CCI





Data cutoff date: March 30, 2020

Single doses of 200 mg LOXO-305 were investigated in a study in healthy volunteers (LOXO-BTK-20014, Pilot Food Effect study) in which the PK was determined. Following a single dose of 200 mg LOXO-305 to patients or healthy subjects, AUC_{0-8} was similar between the two groups and C_{max} was approximately 35% higher in healthy subjects, as shown in the table below (data on file at the time of protocol amendment 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 ng/mL) for micronuclei induction. Assuming that healthy volunteers have a similar accumulation ratio as

observed in patients, the typical C_{max} at steady state after repeated daily doses of 200 mg would be expected to be CCI ng/mL, well below the NOEL threshold.

1.5. Study Rationale

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

After pre-incubation of microsomes or hepatocytes with LOXO-305, the inhibitory potency of LOXO-305 for CYP3A4 was increased and it also induced the mRNA of CYP3A4. Given the theoretical potential for LOXO-305 to alter the PK of CYP3A4 substrates, a clinical drug interaction study is warranted to determine the extent of any interaction. This study is designed to determine the effect of LOXO-305 on the PK of a CYP3A4 substrate, midazolam when administered as a single oral dose and a single IV dose.

CYP3A4 is abundant in the intestines and orally administered midazolam is subject to both intestinal and hepatic CYP3A metabolism. Intravenous midazolam is metabolized by hepatic CYP3A and not intestinal CYP3A. Oral and IV midazolam has been chosen as a way to examine the inhibitory effect of LOXO-305 on both intestinal and hepatic CYP3A activity.[10]

In non-clinical studies, LOXO-305 was metabolized slowly by human microsomal fractions and hepatocytes. LOXO-305 also weakly inhibited the human OATP1B1 and OATP1B3, which are uptake transporters expressed on hepatocytes, responsible for the hepatic uptake of numerous drugs and endogenous compounds. In order to determine the potential for OATP1B1 and OATP1B3 inhibition following LOXO-305 administration, this study will also assess the effect of single dose and steady state concentrations of LOXO-305 on the plasma PK of endogenous CCI , which are demonstrated endogenous biomarkers of OATP1B1 and OATP1B3 functional activity.[11]

1.6. Risk Assessment

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. The dose of LOXO-305 administered in this study is not anticipated to induce any potential risk to subjects participating in this study as the dose does not exceed the highest dose safely administered in first in human studies.[1] There is a potential risk that multiple doses of LOXO-305 may lead to decreases in white blood cells including neutrophils, lymphocytes, monocytes, and eosinophils. Therefore, to mitigate any potential immunosuppressive risks during the ongoing SARS-CoV-2 (COVID-19) pandemic, subjects will remain in the Clinical Research Unit (CRU) for 100 hours postdose (approximately 5 half-lives) on Day 21 to allow for LOXO-305 elimination. In addition, subject's hematology laboratory results will be reviewed prior to discharge from the CRU. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-305 may be found in the IB.[1] Midazolam is a well-established, sensitive, and selective probe for the CYP3A metabolic pathway. Midazolam is subject to extensive first-pass metabolism by CYP3A located in both the intestine and the liver.[12,10] Its major metabolite, 1'-hydroxymidazolam

(1-OH-midazolam), is formed almost exclusively by CYP3A and is further glucuronidated and excreted in the urine. It follows that inhibition or induction of CYP3A in the small intestine and/or the liver will affect the oral bioavailability of midazolam. Preclinically LOXO-305 inhibits and induces CYP3A in the intestine and/or in the liver, the current study will evaluate midazolam exposure after both IV and oral administration.

The dosing regimen of both the oral and IV dose of midazolam in the current study is consistent with use in DDI studies. Both the oral and IV dose are well below the therapeutic dose of midazolam used for sedation[13,14]; however, sedation is a possible side effect. The potential risk of participating in this study and receiving this drug is well managed by the study set-up and considered negligible.

The safety monitoring practices employed will include AE reporting, vital sign measurements, oxygen saturation measured by continuous pulse oximetry, 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 Objectives

The primary objectives of the study are:

- to assess the effect of multiple oral doses of LOXO-305 on the PK of a single oral dose of midazolam in healthy subjects
- to assess the effect of multiple oral doses of LOXO-305 on the PK of a single IV dose of midazolam in healthy subjects

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- to assess the safety and tolerability of multiple oral doses of LOXO-305 when administered alone, coadministered with a single oral dose of midazolam and coadministered with a single IV dose of midazolam.
- to assess the PK of single and multiple doses of LOXO-305 when given alone or with midazolam in healthy subjects.

2.1.3. Exploratory Objective

The exploratory objective of the study is:

- to assess the effect of a single oral dose of LOXO-305 and steady state LOXO-305 on the PK of endogenous CCI as biomarkers of OATP1B1 and OATP1B3 inhibition in 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 midazolam and its metabolite 1-OH-midazolam following oral and IV single dose administration (as appropriate):

- area under the concentration-time curve from hour 0 to the last measurable concentration (AUC_{0-t})
- area under the concentration-time from time 0 extrapolated to infinity (AUC_{0-inf})
- percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$)
- C_{max}
- t_{max}
- apparent terminal elimination rate constant (λ_z)
- apparent systemic clearance (CL/F; oral midazolam)

- total clearance (CL; IV midazolam)
- apparent plasma terminal elimination half-life ($t_{½}$)
- apparent volume of distribution (V_z/F; oral midazolam)
- V_z (IV midazolam)
- volume of distribution at steady state (V_{ss}; IV midazolam).

2.2.2. Secondary Endpoints

Safety and tolerability will be assessed by monitoring AEs, performing physical examinations and clinical laboratory evaluations, measuring vital signs, oxygen saturation measured by continuous pulse oximetry, and 12-lead ECGs.

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

- AUC_{0-t}
- AUC during a dosing interval (AUC_{tau})
- C_{max}
- concentration observed at the end of the dosing interval (C_{trough})
- t_{max}
- CL/F at steady state ($CL_{,ss}/F$)
- accumulation ratio (R_{AUC}).

2.2.3. Exploratory Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of CCI following single dose and steady-state LOXO-305 (as appropriate): C_{max}, t_{max}, AUC from hour 0 to 24 hours (AUC_{0-24}), and steady state concentration (C_{ss}).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 1, open-label, 2-period, fixed-sequence DDI study to investigate the effect of multiple oral doses of LOXO-305 on the PK of a single oral dose of midazolam and on the PK of a single IV dose of midazolam in healthy subjects. The study will also assess the single and multiple oral dose PK of LOXO-305 and the effect of a single oral dose of LOXO-305 and the effect of LOXO-305 at steady state (following multiple dose administration) on the PK of endogenous CCI as biomarkers of OATP1B1 and OATP1B3 inhibition in healthy subjects.

In Period 1, Day 1, a single 250 µg (0.25 mL of 1-mg/mL solution) IV bolus dose of midazolam will be administered over approximately 30 seconds in the morning following a 10-hour fast prior to dosing and a 4-hour fast postdose. On Day 3, a single 500 µg (0.25 mL of 2-mg/mL syrup) oral dose of midazolam will be administered in the morning following a fast of at least 10 hours prior to dosing and 4 hours postdose. On Day 3, the oral midazolam dose will be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour). Blood samples for concentration of midazolam, 1-hydroxymidazolam (1-OH-midazolam), and CCI in plasma CCI in accordance with the Schedule of Assessments [Appendix 4]).

In Period 2 (starting on Day 5), oral doses of 200 mg LOXO-305 will be administered once daily (QD) for 13 consecutive days (Days 5 through 17) in the morning. On Days 5, 14, 15, and 17 oral doses of 200 mg LOXO-305 will be administered following a fast of at least 10 hours prior to dosing and at least 4 hours postdose. On Day 6 through 13, and Day 16 oral doses of 200 mg LOXO-305 will be administered following a fast of at least 2 hours prior to dosing and 1-hour postdose, with the exception of days where clinical laboratory evaluations are performed. On Days 5 through 14, and Day 16, 200 mg LOXO-305 will be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour). On the morning of Day 15, an oral dose of 200 mg LOXO-305 will be administered 2 hours (± 15 minutes) prior to administering a single 250 µg (0.25 mL of 1-mg/mL solution) IV bolus dose of midazolam. On the morning of Day 17, an oral dose of 200 mg LOXO-305 will be administered first before a single oral 500 µg (0.25 mL of 2-mg/mL syrup) dose of midazolam is administered (within 5 minutes). On Days 15 and 17, LOXO-305 will be administered at the actual time of the Day 1 IV midazolam dose (± 1 hour). Blood samples for concentration of LOXO-305 and CCI in plasma will be collected on Days 5 through 16 (on Day 6, 24 hour postdose sample; in accordance with the Schedule of Assessments [Appendix 4]). Blood samples for concentration of midazolam, 1-OH-midazolam, and LOXO-305 in plasma will be collected on Days 15, 16 (24-hour postdose sample), 17, and 18 (24-hour postdose sample). Additionally, blood samples for concentration of LOXO-305 in plasma will be collected on Days 19, 20, and 21 (up to 100 hours post-LOXO-305 dose on Day 17; in accordance with the Schedule of Assessments [Appendix 4]).

There will be a washout period of 2 days between the IV dose of midazolam and the oral dose of midazolam on Days 1 and 3 (Period 1) and Days 15 and 17 (Period 2), respectively.

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 CRU on Day -1 (Check-in).

Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 21 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. A follow-up phone call will occur for all subjects who received at least 1 dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET. The duration of participation is expected to be approximately 59 days (Screening through follow-up phone call).

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

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

In this study, physical examinations, 12-lead ECGs, vital sign measurements, oxygen saturation measured by continuous pulse oximetry, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, hematology panel, urinalysis (UA; Appendix 2) and recording of concomitant medications will be performed at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 4).

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

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

3.2. Discussion of Study Design

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

This study is designed to determine the effect of LOXO-305 on the PK of a CYP3A4 substrate, midazolam. CYP3A4 is abundant in the intestines and orally administered midazolam is subject to both intestinal and hepatic CYP3A metabolism. Intravenous midazolam is metabolized by hepatic CYP3A and not intestinal CYP3A. Oral and IV midazolam has been chosen as a way to examine the inhibitory effect of LOXO-305 on both

intestinal and hepatic CYP3A activity.[10] Midazolam selection as a substrate is based on previous widespread use as a suitable established marker of CYP3A activity and it is recommended to be used as a CYP3A sensitive probe by the FDA; therefore, assessing the potential inhibitory effect of LOXO-305 on CYP3A4 activity.[15] Multiple doses of LOXO-305 will allow the DDI effect(s) of LOXO-305 on midazolam to be assessed at steady-state, therefore the maximal effect on CYP3A4 will be achieved.

This study is also designed to determine the effect of a single dose of LOXO-305 and steady state (multiple dose administration) LOXO-305 on endogenous CCI [redacted] CCI [redacted] have been demonstrated as endogenous biomarkers of hepatic OATP functional activity in vitro and in vivo.[11] Therefore, the PK of CCI [redacted] CCI will be determined following single and multiple doses of LOXO-305.

The fixed single-sequence design used in this study is typical for drug interaction studies where a relatively small number of subjects are required, because it allows intra-subject comparisons. This study will be open-label because the primary endpoints are not considered subjective.

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

3.3. Selection of Doses in the Study

LOXO-305

Multiple oral doses of 200 mg LOXO-305 QD will be administered on Days 5 through Day 14 to achieve LOXO-305 steady state, ensuring the maximal effect of LOXO-305 when coadministered with midazolam. Daily 200 mg LOXO-305 dosing will continue on Day 15 through Day 17 to maintain steady state of LOXO-305 when coadministered with a single IV dose and a single oral dose of midazolam, respectively. 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, including doses of up to 300 mg QD, no dose-limiting toxicities have been identified in humans.[1]

Midazolam

The selected doses for the IV and oral dose of the probe drug midazolam was based on typical doses for this drug and are considered to be high enough to provide sufficient plasma concentrations to achieve the objectives of the study.

4. SELECTION OF STUDY POPULATION

4.1. Screening Procedures

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

1. Inclusion/Exclusion criteria
2. Informed consent
3. Demographic data
4. Medical history (including review of medication[s])
5. Height, weight, and body mass index (BMI)
6. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
7. Vital sign measurements (including oral temperature, respiratory rate, and supine blood pressure [BP] and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
8. Oxygen saturation measured by pulse oximetry (See Section 7.2.5)
9. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
10. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
11. Screens for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV) core antibody, human immunodeficiency virus (HIV) antibody, and COVID-19 via polymerase chain reaction testing ([PCR] or equivalent (Appendix 2)
12. Hemoglobin A1c (HbA1c) test (Appendix 2)
13. Screen for selected drugs of abuse, including cotinine and alcohol (Appendix 2)
14. Estimated glomerular filtration rate (Appendix 2)
15. Serum pregnancy test (for female subjects only; Appendix 2)
16. Follicle-stimulating hormone (FSH) test (for post-menopausal female subjects only; Appendix 2)
17. Thyroid-stimulating hormone (TSH) test (Appendix 2)

4.2. Check-in Procedures (Day -1)

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

1. Review of inclusion/exclusion criteria
2. Interim medical history, including concomitant medication(s)
3. Weight and BMI

4. Complete physical examination (Section 7.2.6)
5. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
6. Vital sign measurements (including oral temperature, respiratory rate, and supine BP and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
7. Oxygen saturation measured by pulse oximetry (See Section 7.2.5)
8. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)
9. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
10. Screen for COVID-19 via PCR or equivalent (Appendix 2)
11. Screen for selected drugs of abuse, including cotinine and alcohol (Appendix 2)
12. Estimated glomerular filtration rate (Appendix 2)
13. Serum pregnancy test (for female subjects only; Appendix 2)
14. Compliance with concomitant medications and exclusionary restrictions (Section 6)

For subjects to continue their participation in the study, the inclusion/exclusion criteria must continue to be met at Check-in (Day -1 [as appropriate; #1, Section 4.2]). In addition, continued compliance with concomitant medication and other restrictions will be verified.

The Sponsor will review medical history and all screening evaluations for potential subjects prior to enrollment. Prior to dosing, the Sponsor will provide approval of subjects selected for enrollment by the Investigator (or designee).

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

4.3. Inclusion Criteria

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

1. Males, and females of non-childbearing potential, between 18 and 55 years of age, inclusive, at Screening.
2. Within BMI range 18.0 to 32.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, or clinical laboratory evaluations (Appendix 4) at Screening and/or Check-in (Day -1) as assessed by the Investigator (or designee).
4. Female subjects of non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to study drug administration) or post-menopausal (defined as at least 12 months post-cessation of

menses without an alternative medical cause). Post-menopausal status will be confirmed with a screening serum FSH level ≥ 40 mIU/mL. All female subjects must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin; serum quantitative human chorionic gonadotropin tests may be used for confirmation as needed) at Screening and Check-in (Day -1). Female subjects are required to refrain from donation of ova from Check-in (Day -1) until 6 months after administration of study drug.

5. Male subjects who are capable of fathering a child must agree to use 1 of the following methods of contraception from the time of the dose administration through 6 months after the last dose of LOXO-305 administration:
    a. Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1). If documentation is not available, male subjects must follow 1 of the contraception methods below:
        i. Male condom with spermicide, or
        ii. A male subject must ensure that their female partner meets 1 of the following criteria:
            1. intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
            2. established use of oral, implanted, injected, transdermal, intravaginal, or hormonal method of contraception associated with inhibition of ovulation; or
            3. non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to male partner's study drug administration); or
            4. be post-menopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with post-menopausal status.

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

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

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

6. Able to understand and provide written informed consent.

7. Able to comply with all study procedures, including the 21-night stay at the CRU and follow-up phone call.

4.4. Exclusion Criteria

The following will exclude potential subjects from the study:

1. History or presence of any of the following, deemed clinically significant by the Investigator (or designee), and/or Sponsor:
    a. liver disease
    b. pancreatitis
    c. peptic ulcer disease
    d. intestinal malabsorption
    e. cholecystectomy
    f. gastric reduction surgery
    g. history or presence of clinically significant cardiovascular disease:
        i. Myocardial infarction or cerebrovascular thromboembolism within 6 months prior to the first dose administration (Day 1)
        ii. Symptomatic angina pectoris within 6 months prior to the first dose administration (Day 1)
        iii. New York Heart Association Class ≥ 2 congestive heart failure within 6 months prior to the first dose administration (Day 1)
        iv. Congenital prolonged QT syndrome
        v. Ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        vi. Arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention
        vii. Ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)
        viii. Significant screening ECG abnormalities:
            1. left bundle-branch block
            2. second-degree atrioventricular (AV) block, type 2, or third-degree AV block
            3. QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec
            4. ECG findings deemed abnormal with clinical significance by the Investigator (or designee), at Screening, Check-in (Day -1), or prior to dosing on Day 1.

        For these ECG parameters, out-of-range parameters that are not clinically significant (as determined by the Investigator [or designee])

may be repeated twice during Screening, Check-in (Day -1), and predose on Day 1. Note: Repeat ECGs will be permitted up to 2 times to confirm eligibility for study.

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

    For these parameters, out-of-range values that are not clinically significant (as determined by the Investigator [or designee]) may be repeated twice during Screening, Check-in (Day -1), and predose on Day 1. Note: Rechecks of pulse rate, BP values, and oxygen saturation will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked pulse rate and/or BP values and/or oxygen saturation if the values fall within the ranges stated above.
3. Abnormal laboratory values (hematology panel, UA, clinical chemistry panel [fasted at least 8 hours], excluding those further defined in exclusion criteria #5, #6, #7, and #8 below) determined to be clinically significant by the Investigator (or designee), and Sponsor at Screening and/or Check-in (Day -1) as confirmed by repeat assessment.
4. Clinically significant abnormality, as determined by the Investigator (or designee), from physical examination at Check-in (Day -1).
5. Abnormal liver function tests (LFTs), as defined by aspartate aminotransferase, alanine aminotransferase, and serum (total and direct) bilirubin, as well as amylase and lipase above the upper limit of the normal range at Screening or Check-in (Day -1). Rechecks of LFTs, amylase, and lipase will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges.
6. Any clinically significant deviations from normal ranges in creatine kinase unless approved by the Investigator (or designee) and Sponsor. Rechecks of creatine kinase will be permitted up to 2 times to confirm eligibility for study participation if the out-of-range values are stable or trending down and the Investigator (or designee) and the Sponsor deem that the results are not clinically significant and will not impact study conduct.
7. Estimated glomerular filtration rate ≤ 90 mL/minute/1.73m^2 at Screening or Check-in (Day -1) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Out of range estimated glomerular filtration rates that are not clinically significant (as determined by the Investigator [or designee]) may be repeated twice during Screening and Check in (Day -1). Note: Repeat estimated glomerular filtration rate will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on

rechecked estimated glomerular filtration rate if the values fall within the range stated above.

8. Hemoglobin, white blood cell count, and platelet counts below the lower limit of normal range at Screening or Check-in (Day -1). Rechecks of hemoglobin, white blood cell count, and platelet counts will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges.
9. Positive serologic test for HbsAg, HBV core antibody, HCV, or HIV antibody at Screening. Subjects who are positive for HCV by antibody will require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HCV PCR positive or for whom a PCR is unable to be obtained will not be eligible.
10. Positive PCR test (or equivalent) for COVID-19 at Screening or Check-in (Day -1). Further details regarding COVID-19 testing (including procedures who test positive at any time throughout CRU confinement) are specified in a separate document.
11. Subjects with known ongoing alcohol and/or drug abuse within 2 years prior to Screening, or evidence of such abuse as indicated by the laboratory assays for drugs of abuse (including cotinine and alcohol) conducted during Screening and/or at Check-in (Day -1). Tests for drugs of abuse must be negative at both Screening and Check-in (Day -1).
12. Consumption of grapefruit/grapefruit juice or Seville oranges or its juice within 7 days prior to Check-in (Day -1) and through EOT or ET.
13. Consumption of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
14. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET.
15. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
16. Participation in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to the first dose administration (Day 1).
17. Use or intention to use any prescription or over-the-counter medications (including but not limited to any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers (including herbal products such as St. John's wort; with the exception of midazolam administered for the purposes of this study/in accordance with the protocol), strong P-gp inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval, herbal products, natural or herbal supplements, and hormone-replacement therapy [HRT]) within 14 days prior to the first dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
18. History of a major surgical procedure within 30 days prior to Screening.
19. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator (or designee), would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk.

20. Poor peripheral venous access.
21. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
22. Receipt of blood products within 2 months prior to Check-in (Day -1).
23. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET.
24. Significant history or clinical manifestation of any allergic, dermatological, biliary, hepatic, gastrointestinal, renal, metabolic, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), neurological, or psychiatric disorder (as determined by the Investigator [or designee]), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin). Note: subjects with a history of appendectomy and/or hernia repairs will be acceptable.
25. History of diabetes mellitus; HbA1c $\geq$ 6.5%.
26. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).
27. Has previously completed or withdrawn from any other study investigating LOXO-305, and have previously received the investigational product.
28. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator (or designee), and as confirmed by the Sponsor, within the 30 days prior to the first dosing and through EOT or ET.
29. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

4.5. Subject Number and Identification

Subject numbers will consist of 6 digits in which the first set of 3 digits will identify the site and the second set of 3 digits will identify the subject (eg, 001-101). If subjects are withdrawn by the Investigator (or designee) or voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have insufficient PK data may be replaced. Replacement subjects will be assigned a subject number by adding 200 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-301 replaces Subject Number 001-101).

4.6. Removal of Subjects from Study Participation

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

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

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

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

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

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

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

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drug (Table 3). Covance will supply midazolam solution (IV) and syrup (oral).

Table 3 Study Drugs

Study Drug	LOXO-305	Midazolam (intravenous)	Midazolam (oral)
Form[a]	Tablet	Solution	Syrup
Strength	100 mg	1-mg/mL	2-mg/mL
Supplier	Loxo Oncology, Inc.	Covance	Covance
Manufacturer	Bend Research, Inc.	West-Ward Pharmaceuticals Corp.[b]	West-Ward Pharmaceuticals Corp.[b]

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

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

Midazolam (oral and IV) will be stored according to the instructions on the package insert.

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

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

5.2. Study Treatment Administration

In Period 1, Day 1, a single IV bolus dose of 250 µg midazolam administered as 0.25 mL of 1-mg/mL solution will be administered in the morning following a 10-hour fast prior to dosing and a 4-hour fast postdose. On Day 3, a single oral dose of 500 µg midazolam administered as 0.25 mL of 2-mg/mL syrup will be administered in the morning following a 10-hour fast prior to dosing and a 4-hour fast postdose. On Day 3, the oral midazolam dose will be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour).

In Period 2, oral doses of 200 mg (2 × 100 mg tablets) LOXO-305 will be administered QD in the morning for 13 consecutive days (Days 5 through 17). On Days 5, 14, 15 and 17, oral doses of 200 mg LOXO-305 will be administered QD in the morning following a fast of at least 10 hours prior to dosing and at least 4 hours postdose. On Days 6 through 13, and Day 16 oral doses of 200 mg LOXO-305 will be administered QD in the morning following a fast of at least 2 hours prior to dosing and 1-hour postdose, with the exception of days where clinical laboratory evaluations are performed. On Days 5 through 14, and Day 16, LOXO-305 will be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour). On

the morning of Day 15, an oral dose of 200 mg LOXO-305 will be administered 2 hours (± 15 minutes) prior to administering a single 250 µg (0.25 mL of 1-mg/mL solution) IV bolus dose of midazolam. On the morning of Day 17, an oral dose of 200 mg LOXO-305 will be administered first before a single oral 500 µg (0.25 mL of 2-mg/mL syrup) dose of midazolam is administered (within 5 minutes). On Days 15 and 17, LOXO-305 will be administered at the actual time of the Day 1 IV midazolam dose (± 1 hour).

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

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

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

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

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

5.3. Randomization

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 and midazolam will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of LOXO-305 tablets and midazolam oral syrup and midazolam IV solution 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. Midazolam oral syrup and midazolam IV solution will be disposed of by the CRU in accordance with the CRU's standard operating procedures.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

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

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

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

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

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

6.2. Diet, Fluid, and Activity Control

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

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

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

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

While confined at the CRU, subjects will receive a standard diet at scheduled times that do not conflict with other study-related activities. Fasting requirement in relation to dosing are described in Section 3.1 and Section 5.2.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of midazolam, 1-OH-midazolam, LOXO-305, and CCI plasma levels will be collected at the timepoints specified in Appendix 4. The exact time of the study drug administration and the actual time of blood sampling for PK analysis will be recorded on the eCRF.

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

7.1.2. Analytical Methodology

Concentrations of midazolam, 1-OH-midazolam, LOXO-305, and CCI will be determined using validated bioanalytical methods. Specifics of the bioanalytical methods will be provided in a separate document.

7.2. Safety and Tolerability Assessments

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

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

- dosing
- PK blood sampling
- vital 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, oxygen saturation measured by continuous pulse oximetry, or clinical laboratory evaluations, will be recorded throughout the study (ie, from signing of the ICF until EOS [or ET if the subject discontinues from the study and does not complete a follow-up phone call]), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

Unless a subject withdraws consent or is withdrawn from the study and does not complete the follow-up phone call, all subjects must be followed until EOS. Subjects with AEs that are assessed as related to study drug by the Investigator (or designee) which are ongoing at EOS may continue to be followed until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator (or designee) and confirmed by the Sponsor. The Investigator (or designee) should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Sponsor may request that additional safety tests be performed.

Subjects will receive a follow-up phone call 7 days (± 2 days) after EOT or ET to determine if any SAE or drug-related AE has occurred since the EOT or ET visit.

At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator (or designee).

Any event that meets the criteria of a suspected unexpected serious adverse reaction (SUSAR) will be reported to the Institutional Review Board (IRB) according to CRU policy by the Investigator (or designee) and to regulatory authorities by the Sponsor (or Sponsor designee) according to regulatory authority requirements. Refer to Reference Safety Information in the current IB[1] for LOXO-305 for additional safety information.

7.2.2. 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], estimated glomerular filtration rate [Screening and Check-in (Day -1)] and UA) will be collected at the timepoints specified in Appendix 4.

Screens for HCV antibody, HbsAg, HBV 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 who test positive at any time throughout CRU confinement) are specified in a separate document.

A urine drug screen for selected drugs of abuse (including cotinine and alcohol) will be performed at Screening and repeated at Check-in (Day -1) for all subjects. A serum qualitative pregnancy test (female subjects only [serum quantitative may be used for confirmation if needed]) and an FSH test (post-menopausal female subjects only) will be performed at the timepoints specified in Appendix 4.

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

7.2.3. Vital Signs

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

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

When vital sign measurements are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vital sign measurements will be obtained prior to and as close as possible to the scheduled blood draw.

7.2.4. 12-lead Electrocardiogram

A 12-lead ECG (including HR, PR, RR, QRS, and QT interval parameters) will be obtained after the subject has been resting for at least 10 minutes in the supine position at the timepoints specified in Appendix 4. The QT interval will be corrected for 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. Oxygen Saturation Measured by Continuous Pulse Oximetry

Each subject will have a baseline pulse oximetry reading done prior to midazolam administration and will be monitored continuously for approximately 6 hours with a pulse oximeter (oxygen levels as saturation [%]) with readings taken at scheduled timepoints (Appendix 4).

Where the time of monitoring coincides with a blood sampling timepoint, the reading will be taken approximately 15 minutes prior to the scheduled timepoint. Readings may be taken at other times, if deemed necessary by the Investigator (or designee).

Outside of the scheduled timepoints, any oxygen saturation reading deemed clinically significant by the Investigator (or designee) will be documented.

7.2.6. Physical Examination

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

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Sixteen healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. This is a phase 1 study and the sample size is not based upon any formal power calculations but is consistent with previous studies of a similar design. Sixteen subjects are anticipated to be sufficient to provide a reliable estimate of the magnitude and variability of the interaction.

Every attempt will be made to enroll at least 4 subjects of each sex in the study.

8.2. Analysis Populations

8.2.1. 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.

8.3. Pharmacokinetic Analysis

Blood samples for plasma concentration analysis will be collected for the following:

- Midazolam and 1-OH-midazolam:
  - Serial PK blood samples CCI and with LOXO-305 CCI
  - Serial PK blood samples CCI and with LOXO-305 CCI.
- LOXO-305:
  - Serial PK blood samples CCI postdose alone CCI . Additionally, blood samples will be collected on CCI .
  - CCI
- CCI :
  - Serial blood samples CCI
  - Blood samples CCI

Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of midazolam and its metabolite 1-OH-midazolam following oral and IV single dose administration (as appropriate):

AUC_{0-t}	AUC from hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
AUC_{0-inf}	AUC from time 0 extrapolated to infinity, calculated using the formula: $AUC_{0-inf} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant.
$\%AUC_{extrap}$	percentage extrapolation for AUC_{0-inf}
C_{max}	maximum observed plasma concentration
t_{max}	time to maximum observed plasma concentration
λ_z	apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
CL/F	apparent systemic clearance (oral midazolam)
CL	total clearance (IV midazolam)
$t_{½}$	apparent plasma terminal elimination half-life (whenever possible), where $t_{½} = \ln(2)/\lambda_z$
V_z/F	apparent volume of distribution during the terminal phase (oral midazolam)
V_z	volume of distribution (IV midazolam)
V_{ss}	volume of distribution at steady state (IV midazolam)

Wherever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of LOXO-305 following single and multiple dose administration:

AUC_{0-t}	AUC from hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
AUC_{tau}:	area under the concentration-time curve during a dosing interval
$CL_{,ss}/F$:	apparent systemic plasma clearance after oral (extravascular) administration, calculated as Dose/AUC_{tau} (Day 14)
C_{max}:	maximum observed plasma concentration at steady-state
C_{trough}:	concentration observed at the end of the dosing interval
t_{max}:	time to reach C_{max}. If the maximum value occurs at more than one timepoint, t_{max} is defined as the first timepoint with this value
R_{AUC}	accumulation ratio

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of CCI following single dose midazolam (IV

administration), single dose LOXO-305, and steady-state LOXO-305 (as appropriate): C_{max}, t_{max}, AUC from hour 0 to 24 hours (AUC_{0-24}), and C_{ss}.

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.

8.3.1. Descriptive Analysis

Plasma concentrations and PK parameters will be summarized with descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum).

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

8.3.2. Statistical Methodology

The primary analysis planned for this study is a mixed effect model that includes treatment as a fixed effect and subject as a random effect. The analysis will be performed on the ln-transformed midazolam and 1-OH-midazolam PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) and include calculation of least squared (LS) means and the difference between treatment LS means, as well as their corresponding 90% confidence intervals (CIs). The geometric mean ratios and their 90% CIs for each treatment comparison will be constructed using the exponentiation of the difference between LS means and the CIs from the mixed effect model. The ratio of midazolam to 1-OH-midazolam will be summarized.

The same method and model as above will be used to analyze the AUC_{0-24} and C_{max} of CCI parameters.

A steady state analysis will be performed on the ln-transformed C_{trough} concentrations for LOXO-305 using Helmert contrasts.[16] Helmert contrasts are constructed such that each timepoint is compared to the mean of the subsequent timepoints.

8.4. 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, as needed, by treatment and timepoint. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of study drug in each period. No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHO Drug Global B3, September 2019). Adverse events will be coded using MedDRA Version 22.1 (or higher). The incidence of AEs will be presented by severity and by relationship to study drug as determined by the Investigator or designee (Appendix 1 for AE reporting). All TEAEs will be summarized by SOC and PT.

8.5. Data Handling and Record Keeping

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

The Data Management Plan will be approved by the Sponsor.

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

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

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

8.6. Quality Control and Quality Assurance

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

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

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

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

9.2. Site Initiation Visit/Investigator Meeting

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

9.3. Disclosure

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

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

9.4. Monitoring

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

9.5. Institutional Review Board

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

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

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

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

9.6. Informed Consent

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

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

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

9.7. Records

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

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

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

9.8. Reference to Declaration of Helsinki/Basic Principles

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

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

9.9. Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

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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 study drug administration should be reported by the Investigator (or designee) via email to Covance or the Sponsor's Clinical Safety Representative within 24 hours of being notified. Covance or the Sponsor's Clinical Safety Representative will then forward the Pregnancy Form to the Investigator (or designee) for completion.

email: SAEIntake@Covance.com

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and ET study procedures will be performed. The subject or partner should be followed by the Investigator (or designee) until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator (or designee) should notify Covance or the Sponsor's Clinical Safety Representative. At the completion of the pregnancy, the Investigator (or designee) will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as 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

Clinical Chemistry Panel (Fasted):	Hematology Panel:	Other Tests:
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Amylase Aspartate aminotransferase (AST) Bilirubin (direct and total) Blood urea nitrogen Calcium Chloride Cholesterol Creatine kinase Creatinine Glucose Iron Lipase Magnesium Phosphorus Potassium Sodium Total protein Triglycerides Uric acid	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential (percent and absolute): Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Hemoglobin A1c (HbA1c)[b] Thyroid-stimulating hormone (TSH)[b] Estimated glomerular filtration rate[a,d] SARS-CoV-2 (COVID-19) test
		Coagulation Parameters:
		Partial thromboplastin time Prothrombin time International normalized ratio
		Serology:[b]
		Human immunodeficiency virus (HIV) antibody Hepatitis B surface antigen (HBsAg) Hepatitis B virus (HBV) core antibody Hepatitis C virus (HCV) antibody
	Urinalysis:	**For Female Subjects only:**
Urine Drug Screen:[a]	Bilirubin Color and appearance Glucose Ketones Leukocyte esterase Nitrite Occult blood pH and specific gravity Protein Urobilinogen Microscopic examination including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)	Pregnancy test (serum qualitative, serum quantitative may be used for confirmation if needed)[c] Follicle-stimulating hormone (post-menopausal female subjects only)[b]
Including but not limited to the following: Alcohol (ethanol) Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine (metabolite) Methadone Opiates Phencyclidine Cotinine		

a. Performed at Screening and Check-in (Day -1) only.
b. Performed at Screening only.
c. Performed at Screening, Check-in (Day -1), and Day 20//Early Termination (ET) only.
d. Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject:

Assessment	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	8.0	1	8.0
Hemoglobin A1c (HbA1c)	4.0	1	4.0
Midazolam pharmacokinetic (PK) sampling LOXO-305 PK sampling CCI PK sampling	4.0	100[a]	400.0
Clinical laboratory evaluations: Hematology Clinical chemistry[b] Coagulation parameters	 4.0 4.0 3.0	7	77.0
Serum creatinine alone	2.0	6	12.0
Serum pregnancy test (female subjects only)	4.0	3	12.0
Serum follicle-stimulating hormone (FSH; post-menopausal female subjects only)	4.0	1	4.0
		Total:	**517.0 mL**

[a] At PK sampling timepoints where multiple analytes (ie, midazolam, OH-1-midazolam, LOXO-305, or CCI) are assessed, a single blood sample will be taken for analysis (see Appendix 4).
[b] Thyroid stimulating hormone and estimated glomerular filtration rate will be assessed as part of the clinical chemistry sample.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 550 mL.

Appendix 4: Schedule of Assessments

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Period 1				Period 2																Clinic Discharge/ EOT/ET[y]	Follow-up Phone Call (EOS)
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	7 (±2) days post EOT/ET[aa]
Confined to the CRU		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion/Exclusion Criteria	X	X																						
Informed Consent	X																							
Demographics	X																							
Medical History	X	X[b]																						
Height/Weight/BMI	X[c]	X[c]																						
Physical Examination[d]		X																					X	
12-lead ECG[e]	X	X	X		X		X				X				X		X		X				X	
Vital Signs[f]	X[g]	X[g]	X		X		X				X				X		X		X				X[g]	
Oxygen Saturation Measured by Pulse Oximetry[h]	X	X	X		X												X		X				X	
HDYF? Inquiry[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Midazolam IV Dosing[k]			X														X							
Midazolam Oral Dosing[l]					X														X					
LOXO-305 Dosing[m]							X	X	X	X	X	X	X	X	X	X	X	X	X					
CCI																								

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Period 1				Period 2																Clinic Discharge/ EOT/ET[y]	Follow-up Phone Call (EOS)
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	7 (±2) days post EOT/ET[aa]
CCI																								
Clinical Laboratory Evaluations[r]	X	X			X				X							X		X				X[z]	X[z]	
Estimated Glomerular Filtration Rate	X	X																						
Serum Creatinine[s]			X	X	X	X	X		X		X		X			X								
Hepatitis and HIV Screen	X																							
COVID-19 Test[t]	X	X																						
HbA1c Test	X																							
Drug Screen[u]	X	X																						
Prior and Concomitant Medications[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[w]	X	X																				X[z]	X[z]	
FSH Test[x]	X																							
TSH Test	X																							

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; COVID-19 = SARS-CoV-2; CRU = Clinical Research Unit; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDYF? = How Do You Feel?; HIV = human immunodeficiency virus; ICF = Informed Consent Form; IV = intravenous; PK = pharmacokinetic; QD = once daily; SAE = serious adverse event; TSH = thyroid-stimulating hormone; UA = urinalysis.

a. For details on study procedures, see Section 7.
b. Interim medical history only.
c. Height collected at Screening only, body mass index based on Screening height.
d. A complete physical examination will be performed at Check-in (Day -1). An abbreviated physical examination will be performed at End of Treatment (EOT; Day 21) or Early Termination (ET).
e. 12-lead electrocardiograms (ECGs) will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws at Screening and Check-in (Day -1), Day 1 (predose, 2 hours after intravenous [IV] midazolam dosing), Day 3 (predose, 2 hours after oral midazolam dosing), Day 5

(predose and 2 hours after LOXO-305 dosing), predose on Day 9 and Day 13, Day 15 (predose, and 2 hours after IV midazolam dosing), Day 17 (predose, and 2 hours after oral midazolam dosing), and at EOT (Day 21) or ET.

f. Vital sign measurements (supine blood pressure [BP], pulse rate, and respiratory rate) will be obtained at Screening and Check-in (Day -1), Day 1 (predose, 2 hours after IV midazolam dosing), Day 3 (predose, 2 hours after oral midazolam dosing), Day 5 (predose and 2 hours after LOXO-305 dosing), predose Day 9 and Day 13, Day 15 (predose, and 2 hours after IV midazolam dosing), Day 17 (predose, and 2 hours after oral midazolam dosing), and at EOT (Day 21) or ET. 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.
g. Oral temperature will be obtained at Screening, Day -1, and at EOT (Day 21) or ET.
h. Oxygen saturation measured by pulse oximetry will be measured at Screening, Day -1, and at EOT (Day 21) or ET. On Days 1, 3, and 17, oxygen saturation will be measured by pulse oximetry predose and will be monitored over a 6-hour continuous period postdose, with data collected predose and at 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours and 6 hours postdose. On Day 15, oxygen saturation will be measured by pulse oximetry pre-IV midazolam dose and will be monitored over a 6-hour continuous period post-IV midazolam dose, with data collected pre IV midazolam dose and at 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours and 6 hours post IV midazolam dose.
i. A How Do You Feel? inquiry will be performed at Screening (after the ICF is signed), at Check-in (Day -1), at each postdose vital sign measurements, and at an appropriate time for all other days.
j. Adverse events (AEs) and serious AEs (SAEs) will be collected beginning at informed consent. Adverse events will be recorded throughout the study (ie, from signing of the Informed Consent Form [ICF] until End of Study [EOS], or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed by the Investigator [or designee]) as related to study procedures, or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug are to be recorded. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.
k. On Day 1, midazolam will be administered in the morning as an IV dose following a fast of at least 10 hours prior to and 4 hours postdose. On Day 15, LOXO-305 will be coadministered with an IV dose of midazolam in the morning following a fast of at least 8 hours prior to and 4 hours post-dosing of IV midazolam. On Day 15, LOXO-305 will be administered 2 hours (± 15 minutes) prior to administering an IV dose of midazolam. On Day 15, LOXO-305 should be administered at the actual time of the Day 1 IV midazolam dose (± 1 hour).
l. On Day 3, midazolam will be administered in the morning as an oral dose following a fast of at least 10 hours prior to and 4 hours postdose. On Day 17, LOXO-305 will be coadministered with an oral dose of midazolam in the morning following a fast of at least 10 hours prior to and 4 hours post-dosing of oral midazolam. On Day 17, LOXO-305 will be administered within 5 minutes prior to administering an oral dose of midazolam. On Day 3 oral midazolam should be administered at the actual time of the Day 1 IV midazolam dose (± 1 hour) and on Day 17, LOXO-305 should be administered at the actual time of the Day 1 IV midazolam dose (± 1 hour).
m. On Day 5 through Day 17, LOXO-305 will be dosed QD in the morning. On Day 15, LOXO-305 will be administered 2 hours (± 15 minutes) prior to administering an IV dose of midazolam. On Day 17, LOXO-305 will be administered within 5 minutes prior to administering an oral dose of midazolam. On Days 5, 14, 15, and 17, LOXO-305 will be administered following a fast of at least 10 hours prior to and at least 4 hours postdose (of LOXO-305 and IV midazolam [on Day 15] and LOXO-305 and oral midazolam [on Day 17]). On Day 6, and Day 8 to 13, LOXO-305 will be administered following a fast of at least 2 hours prior to dosing and 1-hour postdose. On Days 7 and 16 when clinical labs will be collected, LOXO-305 will be administered following a fast of at least 8 hours prior to and 1 hour postdose. On Days 5 through Day 17, LOXO-305 should be administered alone at the actual time of the Day 1 IV midazolam dose (± 1 hour).
n. CCI
o.

p. q. 

r. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and urinalysis (UA) will be performed. At ET or EOT, subjects are not required to be fasted prior to clinical laboratory evaluations.
s. Serum creatinine will be collected predose. On days when clinical laboratory evaluations and serum creatinine are collected (ie Days 3, 7, and 14), serum creatinine will be assessed as part of the same sample used for clinical laboratory evaluations.
t. 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 Clinical Research Unit (CRU) confinement, at the discretion of the Investigator (or designee). Tests will be performed by rapid polymerase chain reaction or equivalent.
u. Drugs of abuse urine test, including cotinine and alcohol. Results from the drugs of abuse tests will be used to determine subject eligibility per the inclusion/exclusion criteria.
v. Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 14 days prior to study drug administration for prescription medications and non-prescription medication, will be recorded on the subject's electronic Case Report Form.
w. Female subjects only.
x. Post-menopausal female subjects only.
y. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 21. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital sign measurements, ECG, and abbreviated physical examination results are to be available for review by the Investigator (or designee) prior to subject release from the CRU at the EOT visit (Day 21) 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.
z. Clinical laboratory evaluations and serum pregnancy test (female subjects only) will be performed on the day prior to subject release from the CRU (Day 20) 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).
aa. To be conducted 7 days (± 2 days) following EOT or ET. EOS is defined as when the subject attends the CRU for a follow-up phone call 7 days (± 2 days) after the EOT visit or ET visit to determine if any SAE or study drug-related AE has occurred since the EOT or ET visit. All subjects who received LOXO-305 (including subjects who are terminated early) will receive a follow-up phone call.

bb [redacted]

cc.

dd. Denotes predose sample collection only.

Appendix 5: Protocol Amendment Summary of Changes

Protocol Version 2.0 (dated 11 September 2020) incorporated the following changes in Protocol Version 1.0 (dated 3rd August 2020):

- Additional preliminary data from ongoing studies with LOXO-305 has been added to Section 1.4, *Summary of Clinical Experience*.
- Exclusion criterion #1, subsection *g*, *viii*, and *4*, has been updated to allow out-of-range values for electrocardiogram parameters that are not clinically significant to be repeated twice during Screening, Check-in (Day -1), and predose on Day 1 and repeat ECGs will be permitted up to 2 times to confirm eligibility for study.
- Exclusion criterion #2 has been updated to allow out-of-range values for oxygen saturation that are not clinically significant to be repeated twice during Screening, Check-in (Day -1), and predose on Day 1 and repeat oxygen saturation measurements will be permitted up to 2 times to confirm eligibility for study.
- Exclusion criterion #7 has been updated to allow out-of-range values for estimated glomerular filtration rate that are not clinically significant to be repeated twice during Screening and Check-in (Day -1) and repeat for estimated glomerular filtration rate measurements will be permitted up to 2 times to confirm eligibility for study.
- An additional pharmacokinetic (PK) blood sample will be collected at 5 minutes post-midazolam intravenous (IV) dosing on Day 1 and Day 15.
- The protocol stated that on the morning of Day 15, an oral dose of 200 mg LOXO-305 would be administered 2 hours prior to administering a single 250 µg (0.25 mL of 1 mg/mL solution) IV bolus dose of midazolam. This has been updated to state that when IV midazolam is administered 2 hours after LOXO-305 administration on Day 15, this can be within a window of ± 15 minutes.
- The specified serum creatinine assessment timepoints in Appendix 4, *Schedule of Assessments* on Day 20 (prior to subject release from the clinical research unit if the subject completes the study) and Day 21 (early termination) were erroneously included and have been removed from the table and from footnote ‘s’.
- Footnote ‘h’ of Appendix 4, *Schedule of Assessments* has been clarified to state that on Day 15, oxygen saturation measured by pulse oximetry should be measured relative to the nominal IV midazolam dose timepoint.
- Footnote ‘k’ of Appendix 4, *Schedule of Assessments* incorrectly stated that subjects should fast for 10 hours prior to dosing of IV midazolam; this has been updated to 8 hours prior to dosing of IV midazolam.
- Footnote ‘m’ of Appendix 4, *Schedule of Assessments* incorrectly stated that subjects should fast for 2 hours postdose on Day 7 and Day 16; this has been updated to 1-hour postdose on Day 7 and Day 16.
- Footnote ‘bb’ of Appendix 4, *Schedule of Assessments* stated that PK blood samples for IV midazolam, oral midazolam, and LOXO-305 could be collected within 15 minutes prior to dosing for the predose sampling timepoint; this has been updated to 30 minutes to be consistent with the PK sampling timepoints in footnotes ‘n’, ‘o’, ‘p’, and ‘q’.

Minor updates:

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