Protocol LOXO-BTK-20011

A Phase I, Single-Dose, Randomized, Partially Double-Blind, Placebo- and Positive-Controlled, 3-Way Crossover Study to Evaluate the Effect of LOXO-305 on QTc Interval in Healthy Subjects

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

Sponsor Signatory:
PPD

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Information described herein is confidential and may be disclosed only with the express written permission of the Sponsor.

SPONSOR APPROVAL

I have read the protocol and approve it:

01-Dec-20 | 06:54:53 PST

Date

INVESTIGATOR AGREEMENT

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

01 DEC 2020

Date

STUDY IDENTIFICATION

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SYNOPSIS

Study Title

A Phase I, Single-Dose, Randomized, Partially Double-Blind, Placebo- And Positive-Controlled, 3-Way Crossover Study to Evaluate the Effect of LOXO 305 on QTc Interval in Healthy Subjects

Objectives

The primary objective of the study is to evaluate the effect of a supratherapeutic dose of LOXO-305 on the QTc interval corrected for heart rate (HR) compared with placebo in healthy subjects.

The secondary objectives of the study are:

- to assess the effect of a single supratherapeutic dose exposure of LOXO-305 on other electrocardiogram (ECG) parameters (HR, PR, and QRS intervals) and on T-wave morphology changes compared with placebo in healthy subjects.
- to demonstrate assay sensitivity of the study to detect a small QTc effect using 400 mg oral moxifloxacin as a positive control in healthy subjects.
- to evaluate the pharmacokinetics (PK) of a single supratherapeutic dose of LOXO-305 in healthy subjects.
- to evaluate the safety and tolerability of a single supratherapeutic dose of LOXO-305 in healthy subjects.

Study Design

This is a single-dose, randomized, partially double-blind (for LOXO-305 only, not moxifloxacin), placebo- and positive-controlled, 3-way crossover design study.

All subjects will participate in 3 treatment periods (Treatment Periods 1, 2, and 3); in each treatment period, subjects will receive either a single oral dose of 900 mg LOXO-305 (Treatment A), a single oral dose of 900 mg LOXO-305 matched placebo (Treatment B), or a single oral dose of 400 mg moxifloxacin (Treatment C). All subjects will receive Treatments A, B, and C on 1 occasion during the study. There will be a washout period of at least 10 days between dosing in each period.

Subjects will be randomly assigned to 1 of 6 treatment sequences (eg, ABC), according to the randomization scheme generated by Covance. A total of 30 subjects will be randomized, such that 5 subjects will be assigned to each treatment sequence.

Each treatment (A, B, and C) will be administered orally in the mornings of Day 1, Day 12, and Day 23 following a fast of at least 8 hours prior to and 6 hours after dosing.

Blood samples for the analysis of plasma concentrations of LOXO-305 will be collected for 96 hours after administration of LOXO-305 (Treatment A) and LOXO-305 matched placebo (Treatment B), and for CCI (Treatment C). Additional blood samples will be collected for 96 hours after administration of LOXO-305

(Treatment A) and LOXO-305 matched placebo (Treatment B) and will be stored for future potential and/or exploratory analysis.

Blood samples from Treatment A will be analyzed for concentrations of LOXO-305 in plasma through 96 hours after administration of LOXO-305. Blood samples from Treatment B will be analyzed for concentrations of LOXO-305 in plasma only at the single timepoint taken 2 hours after administration of LOXO-305 matched placebo. Blood samples from Treatment C will be analyzed for concentrations of moxifloxacin in plasma CCI [redacted] Cardiodynamic sampling will be obtained for 24 hours after administration of each dose in all treatments (A, B, and C).

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 33 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Subjects will be dosed on Day 1, Day 12, and Day 23. A follow-up phone call will occur for all subjects who received at least 1 dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET.

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

In this study, physical examinations, standard safety 12-lead ECGs, vital sign measurements, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, hematology panel, urinalysis (UA; Appendix 2), and recording of concomitant medications will be performed at specified times during the study (for specific timepoints and details on each study variable, refer to Appendix 4). Adverse events (AEs) and serious adverse events (SAEs) will be collected beginning at informed consent. Adverse events will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

Study completion is defined as the time of the last subject's follow-up phone call.

Number of Subjects

A total of up to 30 subjects (5 subjects per treatment sequence) will be enrolled to ensure at least 24 evaluable subjects completed all three treatment periods of the study. A sample size

of 24 evaluable subjects will provide at least 90% power to exclude that LOXO-305 causes more than a 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval of the model-predicted QTc effect (placebo-corrected change from baseline (ΔΔ) QTc [ΔΔQTc]) at the observed geometric mean maximum observed plasma concentration (C_{max}) of LOXO-305 in the study. This power is estimated approximately using a paired t-test. The calculation assumes a 1-sided 5% significance level, a small underlying effect of LOXO-305 of 3 msec, and a standard deviation (SD) of the change from baseline (Δ) QTc (ΔQTc) of 8 msec for both LOXO-305 and placebo.

Main Criteria for Inclusion

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

- Between 18 and 55 years of age, inclusive, at Screening
- Within body mass index (BMI) range 18.0 to 32.0 kg/m^2, inclusive at Screening
- In good general health, based on medical history, physical examination findings, vital signs, standard safety 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

Subject will receive each of the following treatments once throughout the study:

Treatment A:

- A single oral dose of 900 mg LOXO-305 (36 × 25-mg tablets, over-encapsulated [9 capsules]), following a fast of at least 8 hours prior to and 6 hours after dosing.

Treatment B:

- A single oral dose of placebo to match 900 mg LOXO-305 (9 capsules), following a fast of at least 8 hours prior to and 6 hours after dosing.

Treatment C:

- A single oral dose of 400 mg moxifloxacin (1 × 400 mg tablet), following a fast of at least 8 hours prior to and 6 hours after dosing.

Duration of Subject Participation in the Study:

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

Length of CRU Confinement: Up to 34 days (Days -1 to 33).

Planned Study Conduct Duration: Approximately 71 days (Screening through follow-up call).

Criteria for Evaluation:

Pharmacokinetics:

Blood samples for the analysis of concentrations of LOXO-305 in plasma will be collected for 96 hours after administration of LOXO-305 (Treatment A) and LOXO-305 matched placebo (Treatment B). Blood samples for analysis of concentrations of moxifloxacin in plasma will be collected for CCI (Treatment C). Additional blood samples will be collected for 96 hours after administration of LOXO-305 (Treatment A) and LOXO-305 matched placebo (Treatment B) and will be stored for future potential and/or exploratory analysis.

Blood samples from Treatment A will be analyzed for concentrations of LOXO-305 in plasma through 96 hours after administration of LOXO-305. Blood samples from Treatment B will be analyzed for concentrations of LOXO-305 in plasma only at the single timepoint taken 2 hours after administration of LOXO-305 matched placebo. Blood samples from Treatment C will be analyzed for concentrations of moxifloxacin in plasma through CCI

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

Cardiodynamic:

Cardiodynamic sampling will be obtained for 1.5 hours prior to dosing and 24 hours after administration of each dose in all treatments (A, B, and C).

Safety:

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

Statistical Methods

Pharmacokinetics:

Plasma concentrations and PK parameters will be summarized with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum). No formal statistical analysis is planned.

Cardiodynamic:

The primary QTc analysis will be based on concentration-QTc modeling of the relationship between the plasma concentrations of LOXO-305 and change-from-baseline QTc using

Fridericia's method (ΔQTcF) or ΔQTc corrected, with the method chosen as primary if a substantial HR effect is observed. The intent is to exclude an effect of placebo-corrected ΔQTc (ΔΔQTc) > 10 msec at clinically relevant plasma levels. If a substantial HR effect (ie, the largest least squares mean ΔΔHR > 10 bpm in the by-time point analysis) is observed, the QT interval will be corrected using several methods (QTcF, individualized heart rate-corrected QT interval [QTcS], and optimized heart rate-corrected QT interval [QTcI]) and the primary endpoint will be ΔQTc with the method that removes the heart rate dependency of QTc in the best way. Placebo-corrected ΔHR, ΔPR, ΔQRS and ΔQTc (ΔΔHR, ΔΔPR, ΔΔQRS and ΔΔQTc) will also be evaluated at each post-dosing timepoint ('by timepoint' analysis). An analysis of categorical outliers will also be performed as secondary analyses for changes in HR, PR, QRS, QTc, T-wave morphology and U-wave presence.

Safety:

All safety assessments, including AEs, SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and standard safety 12-lead ECGs, will be tabulated, and summarized where possible, using descriptive methodology by treatment and, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of study drug on Days 1, 12, and 23. No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve from hour 0 extrapolated to infinity
Δ	change from baseline
ΔΔ	placebo-corrected change from baseline
ADL	Activities of Daily Living
AE	adverse event
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from hour 0 to 24 hours postdose
AUC_{0-inf}	area under the concentration-time curve from hour 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BP	blood pressure
BSEP	bile salt exporter pump
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CI	confidence interval(s)
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent systemic clearance
C_{max}	maximum observed plasma concentration
COVID-19	SARS-CoV-2
C-QT	concentration-QT
CRF	Case Report Form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration

FSH	follicle-stimulating hormone
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDYF?	How Do You Feel?
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone-replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
IC_{90}	concentration required for 90% inhibition
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IgM	immunoglobulin M
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LFT	liver function test
LOWESS	Locally weighted scatter plot smoothing
LS	least squares
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
MRT	mean residence time
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)
PR	PR interval of the ECG
QD	once daily
QRS	QRS interval of the ECG
QT	QT interval of the ECG
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's method

QTcI	Optimized heart rate-corrected QT interval
QTcS	Individualized heart rate-corrected QT interval
RBC	red blood cell(s)
RP2D	recommended Phase 2 dose
RR	RR interval of the ECG
SAD	single ascending dose
SAE	serious adverse event(s)
SAP	Statistical Analysis Plan
SD	standard deviation
SDD	spray-dried dispersion
SE	standard error
SOC	system organ class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
SSS	sum of squared slopes
$t_{1/2}$	apparent plasma terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time to maximum observed plasma concentration
TQT	thorough QT
TSH	thyroid-stimulating hormone
UA	urinalysis
V_z	volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell(s)
WHO	World Health Organization
λ_z	apparent terminal elimination rate constant

1. INTRODUCTION

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

1.1. Background

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

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

1.2. Nonclinical Pharmacokinetics and Toxicology Summary

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

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

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

LOXO-305 was metabolized slowly by human microsomal fractions and hepatocytes. The low rates of metabolism in both these human in vitro systems suggest that LOXO-305 will have low clearance in humans. In vitro data with clone expressed cytochrome P450 (CYP) enzymes and human liver microsomes indicate that CYP3A4 is the primary CYP enzyme that metabolizes LOXO-305. It is also a substrate for direct glucuronidation.

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

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

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

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

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

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

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

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

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

1.3. Potential for Drug-drug Interactions

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

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

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

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

1.4. Summary of Clinical Experience

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

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

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

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

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

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

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

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

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

1.4.1. Safety

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

- In the 324 patients in the Phase 1/2 Monotherapy cohorts, TEAEs reported in ≥ 10% of patients (n = 33 or more) were fatigue (20.1% total, 8.3% related), diarrhea (17.0% total, 8.6% related), and contusion (13.0% total, 9.0% related). Drug-related TEAEs were reported in 156 of 324 patients (48.1%) in the Phase 1/2 Monotherapy cohorts. The most frequently reported drug-related TEAEs for LOXO-305 (those in > 5% of patients overall) were contusion (9.0%), diarrhea (8.6%), and fatigue (8.3%). All other drug-related TEAEs were reported in < 5% of patients (ie, < 17 patients each). Treatment-emergent AEs of severity Grade 3 or 4 were reported in 87 of 324 patients (26.9%) in the Phase 1/2 Monotherapy cohorts, with 41 (12.7%) of these Grade 3 or 4 AEs reported as related to study drug.
- On-study death (death within 28 days of the last dose of study drug) due to a Grade 5 (fatal) AE was reported in 4 of 324 patients (1.2%) in the Phase 1/2 Monotherapy cohorts. One Grade 5 AE, *Enterococcus faecium*-related septic shock, was considered to be related to study drug (further details are provided in the LOXO-305 IB).[1] All other Grade 5 AEs were considered to be not related to study drug; these included pneumonia fungal, shock, and pleural effusion.

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

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

Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20017 study (headache [observed at the 300 mg LOXO-305 dose], and

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

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

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

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

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

1.4.2. Pharmacokinetics

As of September 30, 2020, PK data were available from 181 patients enrolled in the LOXO-BTK-18001 study. Steady-state PK parameters of LOXO-305 in these cancer patients could be derived from data collected on Cycle 1 Day 8 (Figure 1), and are shown in Table 1. These data show that LOXO-305 is absorbed after oral administration with a median time to maximum observed plasma concentration (t_{max}) of approximately 2 hours and low clearance (Table 1). Due to the limited sampling interval (0-8 hours), imputation for the 24-hour sample was made from Cycle 1 Day 8 predose sample, leading to an estimated plasma half-life of approximately 20 hours. Maximum observed plasma concentration and area under the plasma concentration-time curve (AUC) of LOXO-305 showed increase proportional to dose

(Figure 2). Following administration of the recommended Phase 2 dose (RP2D) 200 mg QD, mean trough plasma levels of LOXO-305 exceeded the concentration required for 96% inhibition of BTK in vitro (IC_{50} = CCI , IC_{96} = CCI). Further details may be found in the IB.[1]

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

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

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

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

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

SDTM Transfer: September 30, 2020

CCI

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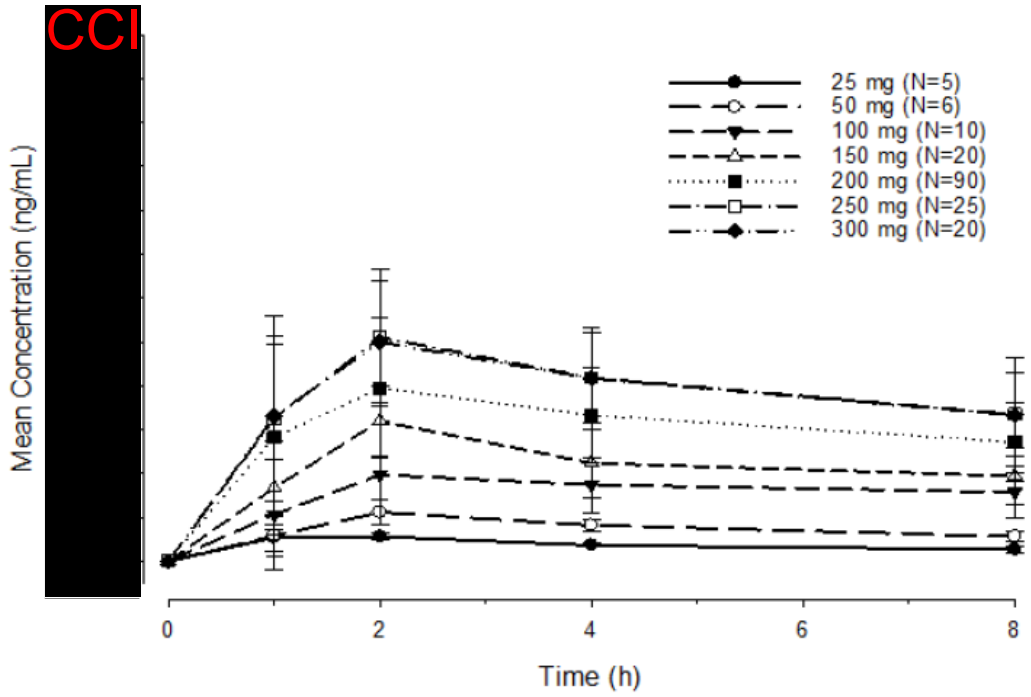
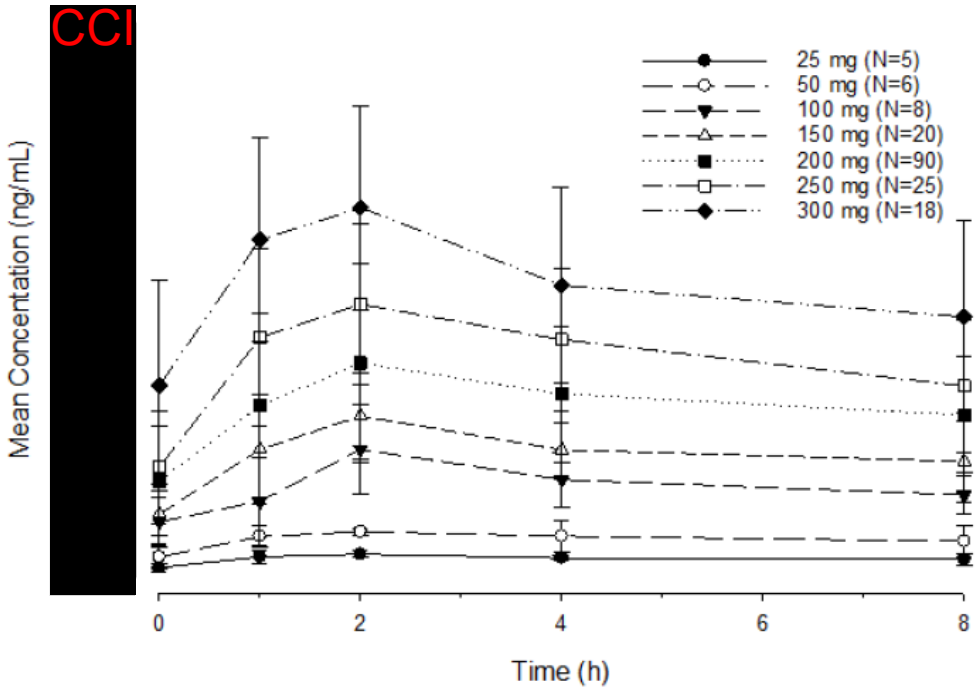

Mean Concentration (ng/mL)
25 mg (N=5)
50 mg (N=6)
100 mg (N=10)
150 mg (N=20)
200 mg (N=90)
250 mg (N=25)
300 mg (N=20)
0
2
4
6
8
Time (h)

CCI


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

SDTM Transfer: September 30, 2020

1.5. Study Rationale

Cardiac safety is a major factor in clinical development given that the effects of new drugs in delaying cardiac repolarization are a common cause for drug withdrawal from the market and delays in, or denial of, regulatory approval for marketing. The potential effect of a drug on cardiac repolarization can be measured as prolongation of the QT interval on electrocardiographic recordings.

Regulatory guidance (International Council for Harmonisation [ICH] E14) has emphasized the need to obtain clear robust data on the effect of new chemical entities on ECG parameters with focus on cardiac repolarization as measured by the QTc duration.[9] Most clinical trials due to insufficient sample size, infrequent sampling of ECG data, or the lack of placebo or positive pharmacologic controls are not adequately powered to overcome the high rate of spontaneous change in QTc duration. The most recent R3 Q&A document updating the ICH E14 guidance[10], specifies that concentration-response analysis, in the correct setting, may serve as the primary basis for decisions to classify the proarrhythmic risk of a new drug.

The study design includes the use of a placebo, a supratherapeutic dose of LOXO-305 (to mimic the exposure in healthy subjects that may occur in the target population under the most extreme circumstances and to assess the effect on cardiac repolarization), and a positive control, moxifloxacin. Modeling the concentration-QT (C-QT) relationship observed during this study will characterize the QT prolongation effect over the observed drug concentration at a supratherapeutic dose of LOXO-305 to assess the drug cardiac effect at therapeutic doses.

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 therapeutic dose of LOXO-305 is 200 mg QD which at steady state has a geometric mean C_{max} of CCI . It is expected that the worst-case scenario during maximal CYP3A4 inhibition will be an increase in the C_{max} of < 2 fold. Thus, the study will target a dose of LOXO-305 that achieves a C_{max} of CCI . The supratherapeutic dose of 900 mg LOXO-305 selected for this study is anticipated to result in a mean C_{max} of approximately CCI based on the data to date from the SAD study (LOXO-BTK-20017) and is not anticipated to induce any potential risk to subjects participating in this study. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-305 may be found in the IB.[1]

Moxifloxacin hydrochloride (HCl) is a synthetic C-8-methoxy-fluoroquinolone antimicrobial agent. The recommended oral dose is 400 mg QD for 5 to 21 days, depending on the specific infection.[11] Following administration of the usual therapeutic dose (400 mg), peak plasma levels occur at approximately 1.5 hours and the elimination half-life of moxifloxacin is about 13 hours. Moxifloxacin prolongs QT interval duration and is used as a positive control in most thorough QT (TQT) studies to determine study sensitivity. The most common AEs seen with moxifloxacin are nausea, diarrhea, headache, and dizziness. The moxifloxacin dosing regimen for this study is within the Food and Drug Administration (FDA)-approved dosing regimen and the risk of moxifloxacin-induced Torsade de Pointes is expected to be minimal when the drug is administered at the recommended dose.

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

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of the study is:

- to evaluate the effect of a supratherapeutic dose of LOXO-305 on the QTc interval corrected for heart rate (HR) compared with placebo in healthy subjects.

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- to assess the effect of a single supratherapeutic dose exposure of LOXO-305 on other ECG parameters (HR, PR, and QRS intervals) and on T-wave morphology changes compared with placebo in healthy subjects.
- to demonstrate assay sensitivity of the study to detect a small QTc effect using 400 mg oral moxifloxacin as a positive control in healthy subjects.
- to evaluate the PK of a single supratherapeutic dose of LOXO-305 in healthy subjects.
- to evaluate the safety and tolerability of a single supratherapeutic dose of LOXO-305 in healthy subjects.

2.2. Endpoints

2.2.1. Primary Endpoint

2.2.1.1. Cardiodynamic

- Placebo-corrected change from baseline (ΔΔ) QTc interval (ΔΔQTc). The default will be ΔΔQTcF with QTc interval corrected for HR using the Fridericia method (QTcF). If a substantial HR effect is observed (ie, the largest least squares [LS] mean ΔΔHR is greater than 10 bpm in the by-time point analysis), other correction methods such as optimized HR-corrected QT interval (QTcI), and individual HR-corrected QT interval (QTcS) will be explored and compared. The method that removes the HR dependence of the QT interval most efficiently will be chosen as the primary correction method for this primary endpoint.

2.2.2. Secondary Endpoints

2.2.2.1. Cardiodynamic

- Change from baseline (Δ) QTcF, HR, PR, QRS intervals (ΔQTcF, ΔHR, ΔPR, and ΔQRS)
- If a substantial HR effect is observed: Change-from-baseline QTcS, and QTcI (ΔQTcS, and ΔQTcI)
- Placebo-corrected change from baseline HR, PR, and QRS (ΔΔHR, ΔΔ PR, ΔΔQRS)

- If a substantial HR effect is observed: Placebo-corrected ΔQTcF, and/or ΔQTcS, and/or ΔQTcI (ΔΔQTcF, ΔΔQTcS, ΔΔQTcI) if not selected as the primary endpoint
- Categorical outliers for QTcF (and QTcS, and QTcI if a substantial HR effect is observed), HR, PR, and QRS
- Frequency of treatment-emergent changes of T-wave morphology and U-wave presence.

2.2.2.2. Pharmacokinetic

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

- AUC from hour 0 to 24 hours postdose (AUC_{0-24})
- AUC from hour 0 to the last measurable concentration (AUC_{0-t})
- AUC from hour 0 extrapolated to infinity (AUC_{0-inf})
- percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$)
- apparent systemic clearance (CL/F)
- C_{max}
- apparent plasma terminal elimination half-life ($t_{½}$)
- t_{max}
- apparent terminal elimination rate constant (λ_Z)
- apparent volume of distribution at the terminal phase (V_Z/F)
- mean residence time (MRT)

In addition, concentrations of moxifloxacin in plasma will be assessed CCI [redacted].

2.2.2.3. Safety

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a single-dose, randomized, partially double-blind (for LOXO-305 only, not moxifloxacin), placebo- and positive-controlled, 3-way crossover design study.

All subjects will participate in 3 treatment periods (Treatment Periods 1, 2, and 3); in each treatment period, subjects will receive either a single oral dose of 900 mg LOXO-305 (Treatment A), a single oral dose of 900 mg LOXO-305 matched placebo (Treatment B), or a single oral dose of 400 mg moxifloxacin (Treatment C). All subjects will receive Treatments A, B, and C on 1 occasion during the study. There will be a washout period of at least 10 days between dosing in each period.

Subjects will be randomly assigned to 1 of 6 treatment sequences (eg, ABC), according to the randomization scheme issued by Covance. A total of 30 subjects will be randomized, such that 5 subjects will be assigned to each treatment sequence (see Table 3 for treatment sequences).

Each treatment (A, B, and C) will be administered orally in the mornings of Day 1, Day 12, and Day 23 following a fast of at least 8 hours prior to and 6 hours after dosing.

Blood samples for the analysis of plasma concentrations of LOXO-305 will be collected for 96 hours after administration of LOXO-305 (Treatment A) and LOXO-305 matched placebo (Treatment B), and CCI [redacted] (Treatment C). Additional blood samples will be collected for 96 hours after administration of LOXO-305 (Treatment A) and LOXO-305 matched placebo (Treatment B) and will be stored for future potential and/or exploratory analysis.

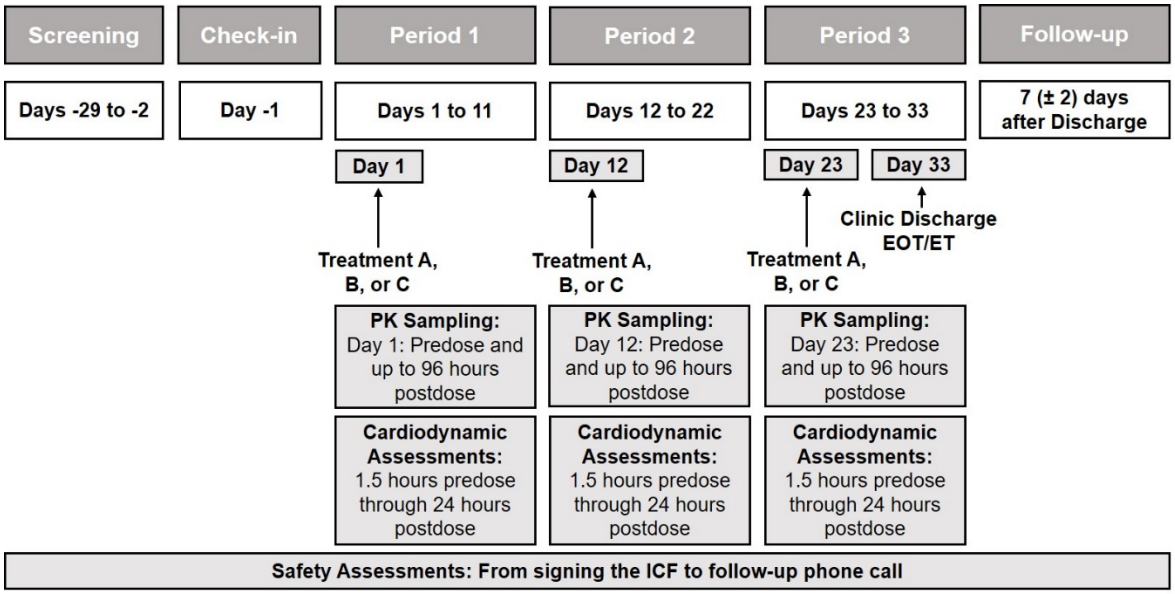
Blood samples from Treatment A will be analyzed for concentrations of LOXO-305 in plasma through 96 hours after administration of LOXO-305. Blood samples from Treatment B will be analyzed for concentrations of LOXO-305 in plasma only at the single timepoint taken 2 hours after administration of LOXO-305 matched placebo. Blood samples from Treatment C will be analyzed for concentrations of moxifloxacin in plasma through CCI [redacted]. Cardiodynamic sampling will be obtained for 24 hours after administration of each dose in all treatments (A, B, and C).

The schematic of the study design is displayed in Figure 3.

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

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

Figure 3: Study Design Schematic



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

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Subjects will be confined at the CRU from the time of Check-in (Day -1) until EOT on Day 33 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Subjects will be dosed on Days 1, 12, and 23. 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 71 days (Screening through follow-up phone call).

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

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

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

3.2. Discussion of Study Design

The study design includes the use of a placebo, a supratherapeutic dose of LOXO-305 to mimic the exposure in healthy subjects that may occur in the target population under the most extreme circumstances and to assess the effect on cardiac repolarization and a positive control, moxifloxacin. Modeling the C-QT relationship observed during this study will characterize the QT prolongation effect over the observed drug concentration of a supratherapeutic dose of LOXO-305 to assess the drug cardiac effect at therapeutic doses.

A randomized crossover design has been selected to minimize assignment bias and to allow each subject to serve as his or her own control, which improves the precision of the estimated treatment differences as well as decreasing the overall number of subjects needed for the study. It will be a partially double-blind study with respect to LOXO-305 and LOXO-305 matched placebo because blinding eliminates confounding by concomitant interventions and biased safety findings, thus eliminating the possibility that the observed effects of intervention are because of differential use of other treatments or biased expectations regarding safety.

Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions. Moxifloxacin as a single 400-mg dose is a standard positive control to be used in QT studies to assess assay sensitivity. This product has been shown to produce a peak QTc prolongation ranging from 10 to 15 msec in crossover design studies,[12,13] with a mean QTc prolongation of about 5 msec. Hence, moxifloxacin-induced changes in ventricular repolarization, when compared to the placebo treatment in healthy subjects, will be used to evaluate assay sensitivity.[13,11]

The sampling scheme is expected to adequately characterize the LOXO-305 exposure-response relationship including hysteresis and late effects and diurnal variability, and the washout period of at least 10 days between each treatment period is considered sufficient to prevent carryover effects of the treatments.

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

3.3. Selection of Doses in the Study

3.3.1. LOXO-305

A single dose of LOXO-305 (900 mg) has been selected as a supratherapeutic dose to provide a single-dose C_{max} that is approximately 2-fold greater than that of the steady-state C_{max} of LOXO-305 at its RP2D in cancer patients, specifically 12860 ng/mL. This target concentration of 12860 ng/mL is 2-fold greater than the geometric mean of CCI from the dosage of 200 mg QD as shown in Table 1. The approximate 2-fold greater C_{max} planned for this study, relative to the steady-state C_{max} in cancer patients, is to account for factors that may reduce the clearance and increase the levels of LOXO-305, for example disease states, or concomitant use of drugs that inhibit the metabolism of LOXO-305. LOXO-305 is metabolized by CYP3A4; emerging data at the time of development of this protocol indicate

that the strong CYP3A4 inhibitor itraconazole caused an approximate 34% increase in LOXO-305 exposure (AUC_{0-t}), but other factors such as hepatic impairment or other settings could make the increase in LOXO-305 exposure larger. Testing plasma concentrations approximately 2-fold higher than geometric mean C_{max} in cancer patients is therefore anticipated to represent a "worst case" supra-therapeutic exposure. The dose of 900 mg LOXO-305 was selected based upon data from the ongoing LOXO-BTK-20017 SAD Study and is expected to achieve a mean C_{max} of approximately CCI .

Single doses of 300 mg, 600 mg, 800 mg, and 900 mg LOXO-305 have been administered to healthy volunteers in Study LOXO-BTK-20017. Preliminary safety and tolerability analysis showed no clinically significant abnormal findings in vital signs and ECG data. Treatment-emergent AEs reported following LOXO-305 administration in healthy volunteers in the LOXO-BTK-20017 study (headache [observed at the 300 mg LOXO-305 dose], and headache [x2], intermittent headache, and petechial rash left thigh [observed at the 900 mg LOXO-305 dose]), were all Grade 1 in severity. One instance of headache observed at the 300 mg LOXO-305 dose and 1 instance observed at the 900 mg LOXO-305 dose, the intermittent headache, and the petechial rash left thigh were considered to be related to LOXO-305. All five AEs were reported by 4 subjects and resolved within 2 hours to 5 days of onset (preliminary data on file at the time of this protocol's development).

3.3.2. Moxifloxacin

A single 400-mg dose is a standard positive control to be used in QT studies. This product has been shown to produce a peak QTc prolongation ranging from 10 to 15 msec in crossover design studies[12,13], with a mean QTc prolongation of approximately 5 msec which is the threshold of regulatory concern. Hence, moxifloxacin-induced changes in ventricular repolarization, when compared to the placebo treatment in healthy subjects, will be used to evaluate assay sensitivity.[13,11] If the slope of the moxifloxacin plasma concentration/ΔQTc relationship is statistically significant at the 10% level in a 2-sided test and the lower bound of the 2-sided 90% confidence interval (CI) of the predicted QT effect at the observed geometric C_{max} of the 400 mg dose is above 5 msec, assay sensitivity will be deemed to have been demonstrated. The dosing regimen for moxifloxacin in this study is within the FDA-approved dosing regimen.

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. Standard safety 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.3.4)
7. Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, and supine blood pressure [BP] and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.3.3)
8. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.3.1)
9. Clinical laboratory evaluations (Section 7.3.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
10. Screens for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV) immunoglobulin M (IgM) core antibody, human immunodeficiency virus (HIV) antibody, and SARS-CoV-2 (COVID-19) via polymerase chain reaction (PCR) testing or equivalent (Appendix 2)
11. Hemoglobin A1c (HbA1c) test (Appendix 2)
12. Urine drug screen for selected drugs of abuse (including cotinine) and alcohol screen (breath or urine; Appendix 2)
13. Estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 2)
14. Serum pregnancy test (for female subjects only; Appendix 2)
15. Follicle-stimulating hormone (FSH) test (for post-menopausal female subjects only; Appendix 2)
16. Thyroid-stimulating hormone (TSH) test (Appendix 2)

4.2. Check-in Procedures (Day -1)

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

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

4. Complete physical examination (Section 7.3.5)
5. Standard safety 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.3.4)
6. Vital sign measurements (including body temperature, respiratory rate, oxygen saturation, and supine BP and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.3.3)
7. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.3.1)
8. Clinical laboratory evaluations (Section 7.3.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
9. Screen for COVID-19 via PCR test (or equivalent; Appendix 2)
10. Urine drug screen for selected drugs of abuse (including cotinine) and alcohol screen (breath or urine; Appendix 2)
11. eGFR calculated using the CKD-EPI equation (Appendix 2)
12. Serum pregnancy test (for female subjects only; Appendix 2)
13. Compliance with concomitant medications and exclusionary restrictions (Section 6)

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

The Sponsor will review medical history and all screening evaluations for potential subjects prior to Check-in (Day -1). Prior to dosing, the Sponsor will provide approval of subjects selected for enrollment by the Investigator (or designee).

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

4.3. Inclusion Criteria

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

1. Males, and females of non-childbearing potential, between 18 and 55 years of age, inclusive, at Screening.
2. Within BMI range 18.0 to 32.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, standard safety 12-lead ECG, vital sign measurements, or clinical laboratory evaluations (Appendix 4) at Screening and/or Check-in (Day -1) as assessed by the Investigator (or designee).
4. Female subjects of non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to Day 1) or post-menopausal (defined as at least 12 months post-cessation of menses without an

alternative medical cause). Post-menopausal status will be confirmed with a screening serum FSH level consistent with post-menopausal status per the laboratory's reference ranges. All female subjects must have a negative qualitative serum pregnancy test (serum human chorionic gonadotropin; serum quantitative human chorionic gonadotropin tests may be used for confirmation as needed) at Screening and Check-in (Day -1). Female subjects are required to refrain from donation of ova from Check-in (Day -1) until 6 months after Day 23 (or last administration of study drug if subject terminates from the study early).

5. Male subjects who are capable of fathering a child must agree to use 1 of the following methods of contraception:
    a. Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1), or
    b. If documentation of surgical sterilization is not available, male subjects must follow 1 of the contraception methods below from Day 1 through 6 months after Day 23 (or last administration of study drug if subject terminates from the study early):
        i. Male condom with spermicide, or
        ii. A male subject must ensure that their female partner meets 1 of the following criteria:
            1. intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®); or
            2. established use of oral, implanted, injected, transdermal, intravaginal, or hormonal method of contraception associated with inhibition of ovulation; or
            3. non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to Day 1 for male partner); or
            4. be post-menopausal with amenorrhea for at least 1 year prior to Day 1 and FSH serum levels consistent with post-menopausal status.

    Male subjects who practice true abstinence because of a lifestyle choice (ie, do not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence by a female partner (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject is abstinent at the time of signing the ICF but becomes sexually active from Check-in (Day -1) through 6 months after Day 23 (or last administration of study drug if subject terminates from the study early), he must agree to use contraception as described above.

    For male subjects, sexual intercourse with female partners who are pregnant, or breastfeeding should be avoided from Check-in (Day -1) through 6 months after Day 23 (or last administration of study drug if subject terminates from the study

early), unless the male subject uses a condom with spermicide. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 6 months after Day 23 (or last administration of study drug if subject terminates from the study early).

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

6. Able to swallow multiple capsules.
7. Able to understand and provide written informed consent.
8. Able to comply with all study procedures, including the 33-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. allergy to band aids, adhesive dressing, or medical tape
    b. seizure(s)
    c. liver disease
    d. pancreatitis
    e. peptic ulcer disease
    f. intestinal malabsorption
    g. cholecystectomy
    h. gastric reduction surgery
    i. history or presence of clinically significant cardiovascular disease:
        i. myocardial infarction or cerebrovascular thromboembolism or transient ischemic attack, pacemaker within 6 months prior to Day 1
        ii. symptomatic angina pectoris or unstable angina within 6 months prior to Day 1
        iii. congestive heart failure ≥ stage 2 per New York Heart Association Classification, cardiomyopathy, or pulmonary hypertension within 6 months prior to Day 1
        iv. cardiac surgery revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)
        v. atrial fibrillation, flutter, non-sustained or sustained ventricular tachycardia, other arrhythmias, or ventricular fibrillation sick sinus syndrome, second- or third-degree atrioventricular block within 6 months prior to Day 1

vi. personal or family history of sudden death or congenital prolonged QT syndrome; unexplained syncope or syncope within the last 3 years regardless of etiology; or history of Torsade's de Pointes

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

viii. arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention within 6 months prior to Day 1

ix. ECG abnormalities at Screening*, Check-in (Day -1), or predose on Day 1, including, but not limited to:

1. complete left bundle-branch block or right bundle branch block or intraventricular conduction delay with QRS > 110 msec
2. second degree atrioventricular (AV) block, type 2, or third-degree AV block
3. QTcF is > 440 msec
4. QRS interval > 110 msec; result will be confirmed by manual over-read
5. PR interval > 220 msec
6. HR < 50 bpm or > 90 bpm
7. Electrographically significant abnormalities that might interfere with ECG analysis including evidence of a previous myocardial infarction, left ventricular hypertrophy, flat T waves (particularly in the inferior leads) or more than minor non-specific ST-T wave changes.

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

2. Subjects with out-of-range, at-rest (ie, supine for at least 5 minutes) vital sign measurements at Screening, Check-in (Day -1), or prior to dosing on Day 1. Out-of-range vital sign measurements are defined as:

a. body temperature > 37.5°C;

b. pulse rate < 50 or > 90 beats per minute (bpm);

c. systolic BP < 89 or > 139 mmHg;

d. diastolic BP < 50 or > 89 mmHg;

e. oxygen saturation < 95% (room air).

Subjects with out-of-range values for these parameters that are not clinically significant will be permitted to have vital sign measurements repeated up to 2 times during Screening, Check-in (Day -1), and predose on Day 1 to confirm eligibility for

study participation if the repeat value(s) are normal/fall outside of the ranges stated above.

3. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator (or designee), or mentally or legally incapacitated or has significant emotional problems at the time of the Screening visit or expected during the conduct of the study.
4. Clinically significant abnormality, as determined by the Investigator (or designee), from physical examination at Check-in (Day -1).
5. Abnormal laboratory values (hematology panel, UA, clinical chemistry panel [fasted at least 8 hours]) that are clinically significant excluding those further defined in exclusion criteria #6, #7, #8, #9, #10, #11, and #12 at Screening and/or Check-in (Day -1). Subjects with out-of-range clinical laboratory results that are not clinically significant (excluding those further defined in exclusion criteria #6, #7, #8, #9, #10, #11, and #12) may have laboratory assessments repeated at the Investigator (or designee)'s discretion up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall within normal ranges or are stabilizing.
6. Abnormal liver function tests (LFTs) as defined by aspartate aminotransferase, alanine aminotransferase, and serum (total and direct) bilirubin, as well as amylase, or lipase above the upper limit of the normal range per the laboratory's reference ranges at Screening or Check-in (Day -1). Subjects with out-of-range LFTs, amylase, and lipase values above the upper limit of normal that are not clinically significant will be permitted to have LFTs, amylase, or lipase assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall within normal ranges.
7. Creatine kinase values above the upper limit of the normal range per the laboratory's reference ranges that are clinically significant at Screening or Check-in (Day -1). Subjects with out-of-range creatine kinase values that are not clinically significant will be permitted to have the creatine kinase assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) are stable or normalizing.
8. Estimated glomerular filtration rate (eGFR) $\leq$ 80 mL/minute/1.73m^2 calculated using the CKD-EPI equation at Screening or Check-in (Day -1). Subjects with out-of-range eGFR values that are not clinically significant will be permitted to have eGFR assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall above the range stated above.
9. Hemoglobin below the lower limit of normal range per the laboratory's reference ranges at Screening or Check-in (Day -1). Subjects with out-of-range hemoglobin that is not clinically significant will be permitted to have hemoglobin assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall above the lower limit of normal range or are normalizing.
10. Potassium values < 4.0 mEq/L at Screening or Check-in (Day -1). Subjects with potassium values < 4.0 mEq/L that are not clinically significant will be permitted to

have potassium assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall above the range stated above or are normalizing.

11. Calcium values < 8.5 mg/dL at Screening or Check-in (Day -1). Subjects with calcium values < 8.5 mg/dL that are not clinically significant will be permitted to have calcium assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall above the range stated above or are normalizing.
12. Magnesium levels < 2.0 mEq/L at Screening or Check-in (Day -1). Subjects with magnesium values < 2.0 mEq/L that are not clinically significant will be permitted to have magnesium assessments repeated up to 2 times during Screening and Check-in (Day -1) to confirm eligibility for study participation if the repeat value(s) fall above the range stated above or are normalizing.
13. HbA1c ≥ 6.5% at Screening. Subjects with out-of-range HbA1c values that are not clinically significant will be permitted to have HbA1c assessments repeated up to 2 times during Screening to confirm eligibility for study participation if the repeat value(s) fall below the range stated above.
14. Positive serologic test for HBsAg, HBV IgM core antibody, HCV antibody, or HIV antibody at Screening. Subjects who are positive for HBV IgM core antibody or HCV antibody require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HBV core antibody or HCV antibody positive or for whom a PCR is unable to be obtained will not be eligible.
15. Positive PCR test (or equivalent) for COVID-19 at Screening or Check-in (Day -1). Further details regarding COVID-19 testing (including procedures for subjects who test positive at any time throughout CRU confinement) are specified in a separate document.
16. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).
17. Significant history or clinical manifestation of any allergic, dermatological, biliary, hepatic, gastrointestinal, renal, metabolic, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or heart failure), neurological, or psychiatric disorder (as determined by the Investigator [or designee]), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin). Note: subjects with a history of appendectomy and/or hernia repairs will be acceptable.
18. 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.
19. History of a major surgical procedure within 30 days prior to Screening.
20. 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).

21. Use of tobacco, smoking-cessation products, or products containing nicotine and e-cigarettes (nicotine and non-nicotine), within 3 months prior to Screening and through EOT or ET.
22. Use or intention to use any prescription or over-the-counter medications (including but not limited to any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers [including herbal products such as St. John's wort], CYP2C8 substrates, strong P-gp inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval [with the exception of moxifloxacin administered for the purposes of this study/in accordance with the protocol], vitamin supplements, herbal products, natural or herbal supplements, and hormone-replacement therapy [HRT]) from 14 days prior to Day 1 or 5 half-lives (if known, whichever is longer) through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
23. 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.
24. Consumption of alcohol- or caffeine-containing foods or beverages within 5 days prior to Check-in (Day -1) and through EOT or ET.
25. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
26. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator (or designee), within the 30 days prior to Day 1 and through EOT or ET.
27. Participation in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to Day 1.
28. Has previously received LOXO-305 in any other study investigating LOXO-305, within 30 days prior to Day 1.
29. History within the past 2 months of strenuous exercise (eg, marathon running) and is unwilling to refrain from strenuous exercise from 7 days prior to Day -1 (Check-in) through EOT or ET.
30. Poor peripheral venous access.
31. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
32. Receipt of blood products within 2 months prior to Check-in (Day -1).
33. 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).

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

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

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

4.6. Removal of Subjects from Study Participation

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

- change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety
- occurrence of AEs
- QTcF interval > 500 msec, and on recheck within 30 minutes and confirmed by the core ECG laboratory, on any scheduled standard safety ECG or at any time an unscheduled ECG for safety was deemed necessary by the Investigator (or designee), or an increase > 75 msec from baseline not associated with significant hypokalemia
- occurrence of pregnancy
- non-compliance with study restrictions
- intake of non-permitted concomitant medication that might affect subject safety or study assessments/objectives, etc.

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

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

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

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

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of LOXO-305. Covance will procure adequate quantities of LOXO-305 matched placebo, capsules to over-encapsulate LOXO-305 and for LOXO-305 matched placebo, and moxifloxacin.

Table 2: Study Drugs

Study Drug	LOXO-305	Moxifloxacin	LOXO-305 Matched Placebo
Form[a]	Tablet[b]	Tablet	Powder-filled Capsule[b]
Strength	25 mg	400 mg	N/A
Supplier	Loxo Oncology, Inc.	Covance	Covance
Manufacturer	Bend Research, Inc.	To be confirmed[c]	Covance

[a] Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug(s).
[b] Tablets will be over-encapsulated and matching capsules will be filled with placebo powder by Covance to maintain study blind.
[c] The manufacturer will be confirmed by the site at the time of drug procurement.

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

LOXO-305 matched placebo powder and moxifloxacin will be supplied by Covance and stored according to the instructions in the package insert and/or label.

Size 0 light blue capsules to over-encapsulate LOXO-305 tablets and LOXO-305 matched placebo powder will be supplied by Covance.

LOXO-305 tablets will be over-encapsulated (with 4 tablets of LOXO-305 being placed in each capsule) and LOXO-305 matched placebo powder will be encapsulated according to Covance CRUs Standard Operating Procedures (SOPs) and relevant processes.

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

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

5.2. Study Treatment Administration

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

Treatment A:

- A single oral dose of 900 mg LOXO-305 (36 × 25-mg tablets, over-encapsulated [9 capsules]), following a fast of at least 8 hours prior to and 6 hours after dosing.

Treatment B:

- A single oral dose of placebo to match 900 mg LOXO-305 (9 capsules), following a fast of at least 8 hours prior to and 6 hours after dosing.

Treatment C:

- A single oral dose of 400 mg moxifloxacin (1 × 400 mg tablet), following a fast of at least 8 hours prior to and 6 hours after dosing.

All study drugs will be administered with approximately 240 mL of water. An additional volume of up to approximately 240 mL of water may be administered if needed. Water will be restricted for 1-hour predose and 1-hour postdose, with the exception of water administered for dose administration.

Each unit dose will be prepared by qualified CRU staff.

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

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

Following dosing, subjects will remain lying down or sitting and awake for the first 7 hours of the 24-hour postdose cardiodynamic ECG monitoring period, as the QT-RR relationship is different during sleep. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli (ie, TV, loud radio, interactions with other subjects, etc.) for at least 10 minutes before and 5 minutes during the ECG extraction to allow for quality ECG extraction. In the event that an AE(s) occurs at any time during cardiodynamic ECG recordings, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

5.3. Randomization

Subjects will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number (in accordance with the requirements in Section 4.5 and the randomization scheme generated by Covance) prior to the time of the first dose, different from the screening number, and will receive the corresponding product according to the randomization scheme generated by Covance.

Subjects will be randomly assigned to 1 of 6 treatment sequences (Table 3), according to the randomization scheme issued by Covance.

Table 3: Treatment Sequences

		Treatment Period		
		1	**2**	**3**
Treatment Sequence	**1**	A	B	C
	2	B	C	A
	3	C	A	B
	4	A	C	B
	5	C	B	A
	6	B	A	C

The randomization scheme and corresponding subject assignment will be available only to the CRU pharmacy staff that is preparing the doses of LOXO-305, LOXO-305 matched placebo, and moxifloxacin. These CRU pharmacy staff will not be involved in any other aspect of the study including administration of the doses to subjects. The randomization scheme and corresponding subject assignment will also be available to the bioanalytical laboratory as sample analysis will be treatment-dependent (ie, different method, and dilutions depending on the treatment). It will not be made available to the Sponsor, subjects, members of the CRU staff responsible for the monitoring and evaluation of safety assessments (including the members of the CRU staff responsible for ECG reading).

5.4. Blinding

This is a partially double-blind study with respect to LOXO-305 and LOXO-305 matched placebo, of which LOXO-305 will be supplied as tablets, which will be over-encapsulated by the CRU pharmacy staff and placebo will be supplied as a powder to fill capsules by the CRU pharmacy staff to maintain the blind. Moxifloxacin treatment (positive control) will be administered in an open-label fashion.

5.4.1. Procedures for Breaking the Blind Prior to Study Completion

One set of sealed envelopes containing the randomization code will be supplied to the Investigator (or designee) at each site at the start of the study.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject.

In the event of a medical emergency, it is requested that the Investigator (or designee) make every effort to contact the Sponsor prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the Investigator (or designee) for that subject only. In the event that the medical emergency is one in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects who have received study drug(s). The unblinding will be properly documented in the study file.

In all cases where the randomization code is broken, the Investigator (or designee) should record the date and reason for code breaking.

At the end of the study, envelopes will be retained or destroyed according to relevant Covance CRU SOPs and procedures unless specified otherwise by the Sponsor.

5.4.2. Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, and the database is officially locked.

Preliminary data and any data received from the bioanalytical laboratory prior to the clinical database lock will be blinded (using dummy IDs).

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, LOXO-305 matched placebo, and moxifloxacin, as appropriate, will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies (including LOXO-305 tablets, excipient [for LOXO-305 matched placebo], capsules to over-encapsulate LOXO-305 and excipient [for LOXO-305 matched placebo powder], and moxifloxacin tablets) received from the Sponsor or procured by Covance. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

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

At the completion of the study, all unused LOXO-305 tablets will be disposed of by the CRU in accordance with the CRU's SOPs and local/state/federal guidelines governing waste disposal of investigational drugs, following the Sponsor's written authorization. Placebo powder and moxifloxacin tablets and will be disposed of by the CRU in accordance with the CRU's SOPs.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

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

All prescription medications and over-the-counter medications, including but not limited to: moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers (including herbal products such as St. John's wort), CYP2C8 substrates, strong P-gp inhibitors, proton pump inhibitors, antacids, H_2-receptor antagonists, and drugs that prolong QT/QTc interval (with the exception of moxifloxacin administered for the purposes of this study/in accordance with the protocol), herbal products, vitamin supplements, natural or herbal supplements, and HRT are prohibited for 14 days or 5 half-lives (if known), whichever is longer, prior to Day 1 and through EOT or ET, unless deemed acceptable by the, Investigator (or designee), and Sponsor. Any medication taken by a subject during the course of the study, including details of its dosage, administration, and the reason for its use, will be documented in the eCRF.

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

6.2. Diet, Fluid, and Activity Control

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

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

Consumption of alcohol- or caffeine-containing foods or beverages within 5 days prior to Check-in (Day -1) and through EOT or ET will not be allowed.

On Days 1, 12, and 23, subjects will be fasted for at least 8 hours prior to dosing through 6 hours postdose. Water will be restricted for 1 hour prior to and 1 hour after dosing, with the exception of water administered for dose administration.

On Days 1, 12, and 23, a light meal will be provided immediately following completion of the cardiodynamic ECG recording at the 6-hour postdose timepoint and a full meal will be provided immediately after the 12-hour postdose timepoints. A snack can also be given just after the 8.5-hour postdose timepoint. Meals and snacks must be scheduled to be completed at least 90 minutes prior to any scheduled ECG (ie, standard safety 12-lead ECG, or cardiodynamic ECG). Otherwise, 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.

Subjects should not have a history within the past 2 months of strenuous exercise (eg, marathon running) and will refrain from strenuous exercise from 7 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).

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of plasma concentrations of LOXO-305, LOXO-305 matched placebo, moxifloxacin plasma levels, and for future potential and/or exploratory analysis 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 and for blood samples collected for future potential and/or exploratory analysis will be provided in a separate Laboratory Manual. The number of blood samples and total blood volume required for PK testing is presented in Appendix 3.

7.1.2. Analytical Methodology

Concentrations of LOXO-305 and moxifloxacin in plasma will be determined using validated bioanalytical methods. For PK samples collected for LOXO-305 matched placebo, only the samples collected 2 hours postdose will be analyzed for concentrations of LOXO-305 or moxifloxacin, as appropriate. Specifics of the bioanalytical methods will be provided in a separate document.

7.2. Cardiodynamic Assessments

7.2.1. Cardiodynamic ECGs (Holter Monitoring)

Holter monitors will be used to collect continuous 12-lead ECG data for the purpose of collecting cardiodynamic ECGs for approximately 25.5 hours, starting at approximately 1.5 hours prior to dosing and at least 24 hours postdose. Recording will be started and stopped at logistically optimal times to ensure that all scheduled time points are collected. Up to 10 replicate 12-lead ECG recordings will be extracted from the continuous Holter recording at the timepoints specified in Appendix 4, prior to the collection of blood samples for PK analysis.

Timing and recording technique for ECGs will be standardized for all subjects. Subjects must be awakened at least 1 hour prior to the start of the cardiodynamic ECGs on the day of dosing and before the ECG recording scheduled at the 24-hour postdose timepoint as specified in Appendix 4.

Following dosing on days where cardiodynamic ECG assessments are performed, subjects will remain lying down or sitting and awake for the first 7 hours of the 24-hour postdose cardiodynamic ECG monitoring period, as the QT-RR relationship is different during sleep. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli (ie, TV, loud radio, interactions with other subjects, etc.) for at least 10 minutes before and 5 minutes during the ECG extraction to allow for quality ECG extraction. In the event that an AE(s) occurs at any time

during cardiodynamic ECG recordings, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

All ECG extraction should occur in a 5-minute time window around the scheduled/nominal time and always precede the PK draw. If targeted ECG timepoints are artefactual or of poor quality, analyzable 10-second ECGs will be extracted as close as possible to the targeted time points.

The 12-lead Holter and ECG equipment will be supplied and supported by ERT. All ECG data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12-lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. ECGs to be used in the analyses will be selected by pre-determined timepoints as defined in the Appendix 4 and will be read centrally by ERT.

The following principles will be followed in ERT's core laboratory:

- ECG readers are blinded to the subject, visit, and treatment allocation
- A limited number of readers will be employed for the study
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader
- The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire subject data set

The following is a brief description of ECG analysis methods utilized by ERT's core laboratory.

7.2.1.1. TQT Plus ECG Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of < 10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

7.2.1.2. Expert-Precision QT Analysis

Expert-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely)
- RR values exceeding or below certain thresholds (biologically unlikely)
- Rapid changes in QT, QTc, or RR from beat-to-beat

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" are performed using COMPAS software. All low confidence beats are reviewed manually and adjudicated using pass-fail criteria. The final QC assessment is performed by a cardiologist. The beats found acceptable by manual review are included in the analysis. The median QT, QTc, and RR value from each extracted replicate is calculated, and then the mean of all available medians from a nominal timepoint is used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, ie, changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicate at the timepoint. For baseline, the category will be deemed as present if observed in any replicate from all timepoints that constitute baseline. Nominal time of the cardiodynamic ECG recording will be used for the cardiodynamic analysis.

Procedures for ECG extraction and Early Precision QT evaluation at the central ECG laboratory (ERT) will be provided separately.

7.3. Safety and Tolerability Assessments

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

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

- dosing
- ECG extraction (for cardiodynamic assessments)
- PK blood sampling
- vital sign measurements *
- standard safety 12-lead ECGs *
- blood and urine samples for clinical laboratory evaluations
- physical examination

* When vital sign measurements and standard safety 12-lead ECGs are scheduled at the same time as PK blood sampling, the PK blood sampling will be obtained at the scheduled timepoint, and the vital sign measurements followed by standard safety 12-lead ECGs will be obtained prior to and as close as possible to the scheduled PK blood sampling.

7.3.1. Adverse Events

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

Subjects will be asked a non-leading HDYF? question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the timepoints specified in Appendix 4 (ie, at Screening [after the ICF is signed], at Check-in [Day -1], at each postdose vital sign measurement, and at an appropriate time for all other days). Subjects will also be encouraged to voluntarily report AEs occurring at any other time through the EOS.

Adverse events, whether volunteered, identified by the subject's responses to HDYF? inquiries, or noted on physical examination, standard safety ECG, vital sign measurements, or clinical laboratory evaluations, will be recorded throughout the study (ie, from signing of the ICF until EOS [or ET if the subject discontinues from the study and does not complete a follow-up phone call]), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.

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

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

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

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

7.3.2. Clinical Laboratory Evaluations

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

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

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

A urine drug screen for selected drugs of abuse (including cotinine) and an alcohol screen (urine or breath) will be performed at Screening and repeated at Check-in (Day -1) for all subjects.

A serum qualitative pregnancy test (female subjects only [serum quantitative may be used for confirmation, if needed]) and an FSH test (post-menopausal female subjects only) will be performed at the timepoints specified in Appendix 4.

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

7.3.3. Vital Signs

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

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

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

7.3.4. Standard Safety 12-lead Electrocardiogram

A standard safety 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. There will be no significant stimuli such as TV, loud radio, interactions with other subjects. The QT interval will be corrected for HR by Fridericia's ($QTcF = QT/[RR]^{1/3}$) formula. In the event that an AE(s) occur at any time during safety ECG recordings, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

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

In all cases in which a standard safety ECG has a potentially concerning finding (eg, QTcF > 500 msec, increase from baseline QTcF > 75 msec), or an abnormal and potentially clinically significant observation, it will be repeated within 30 minutes and the ECGs will be reviewed independently by the ECG core laboratory or, if not feasible, by a cardiac electrophysiologist prior to any study disposition decisions that do not constitute a patient emergency. The safety ECG data, including all timepoints, will be recorded on the eCRF and used for evaluating general safety of the subjects during study and for evaluation of an AE. The ECG core laboratory analysis will constitute the ECG analysis used for all study decisions as well as the primary ECG analysis for the study.

7.3.5. Physical Examination

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

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

A total of up to 30 subjects (5 subjects per treatment sequence) will be enrolled to ensure at least 24 evaluable subjects completed all three treatment periods of the study. A sample size of 24 evaluable subjects will provide at least 90% power to exclude that LOXO-305 causes more than a 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% CI of the model-predicted QTc effect (ΔΔQTc) at the observed geometric mean C_{max} of LOXO-305 in the study. This power is estimated approximately using a paired t-test. The calculation assumes a 1-sided 5% significance level, a small underlying effect of LOXO-305 of 3 msec, and a standard deviation (SD) of the ΔQTc of 8 msec for both LOXO-305 and placebo. The concentration-QTc analysis method is supported by Darpo et al[14] and Ferber et al[15], and is consistent with the experiences from 25 recent TQT studies.

8.1.1. Determination of Sample Size for Assay Sensitivity

To demonstrate assay sensitivity with concentration-QTc analysis, it has to be shown that the ΔΔQTc of a single dose of 400 mg moxifloxacin exceeds 5 msec (ie, the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTc] should exceed 5 msec). In a similarly designed, recent crossover study with 24 healthy subjects (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the concentration-QTc analysis was 1.24 msec. The within-subject SD of ΔQTcF in the referred study was 5.4 msec based on the by-timepoint analysis. If the effect of moxifloxacin is assumed to be 10 msec, the SE of 1.24 msec corresponds to an effect size of (10-5)/(1.24 ×sqrt[24])= 0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.62 required to guarantee a power of at least 90% in a paired t-test situation with a sample size of 24 evaluable subjects. In other words, based on this calculation, a power of at least 90% for 24 evaluable subjects will be obtained as long as the variability of the ΔQTc, as measured by its within-subject SD, does not exceed 7.1 msec (ie, 132% [= 0.82/0.62] of the 5.4 msec observed in the referred study assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD). The number also agrees with recent recommendations of the FDA, which propose at least 20 subjects. [16]

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

8.2. Analysis Populations

8.2.1. Study Populations

The **QT/QTc population** will consist of all subjects who have received 1 dose of study drug (LOXO-305, moxifloxacin, and placebo) with measurements at baseline as well as on-treatment with at least 1 postdose timepoint with a ΔQTc value. The QT/QTc population will be used for the by-timepoint and categorical analysis of cardiodynamic ECG parameters.

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

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

The **PK/QTc population** will consist of all subjects who are in both the QT/QTc and PK populations with at least 1 pair of postdose PK concentration and ΔQTc data from the same timepoint in at least 1 period as well as subjects in the QT/QTc population who received placebo. The PK/QTc population will be used for the concentration-QTc analysis and assay sensitivity. PK/QTc population will be defined for LOXO-305, for its metabolites, and for moxifloxacin.

8.3. Cardiodynamic Analysis

8.3.1. Baseline

For all continuous ECG parameters from each period, baseline will be the average of the derived ECG intervals from the 3 ECG timepoints prior to treatment administration on Day 1, Day 12, and Day 23. For T-wave morphology and U-wave presence from each period, baseline includes findings observed in any of the replicates from the 3 timepoints prior to dosing on Day 1, Day 12, and Day 23.

8.3.2. QT Correction Methods

The QT and RR value for each beat will be used for HR correction. Twelve-lead ECGs will be extracted in up to 10 replicates from each nominal timepoint. The median value of each parameter from the set of evaluable beats in each extracted replicate will be calculated, and then the mean of all available medians (minimum 3 medians) from the nominal timepoint will be used as the subject's reportable value at that timepoint.

If the largest LS mean peak ΔΔHR after dosing with LOXO-305 is $\leq$ 10 bpm, the HR correction method will be the Fridericia method defined as:

$$QTcF\ (msec) = QT\ (msec)/[RR\ (msec)/1000]^{1/3}$$

If a substantial HR effect is observed, ie, the largest LS mean ΔΔHR larger than 10 bpm in the by-time point analysis, additional QT correction methods may be explored. Since Holter recordings are not collected on Day -1, prior to treatment, additional QT correction method will be derived from Day 1 of the placebo period during both the timepoints of supine rest (QTcS) and from all evaluable QT/RR pairs in the 24-h recording (QTcI). These data will be used to obtain RR interval (HR) and QT data to enable derivation of QTcS, and QTcI, as follows.

1. An individualized HR-corrected QT interval (QTcS) will be calculated from QT/RR data obtained at supine resting timepoints on Day 1 of the placebo period. Based on QT/RR pairs from all subjects, the QTcS correction coefficient will be derived from a linear mixed-effects model: $\log(QT_{ij}) = \log(a_i) + b1_i \times \log(RR_{ij}) + b2_i \times gender_i + b3_i \times \log(RR_{ij}) \times gender_i$ with gender included as a fixed effect for both intercept and slope, and subject included as a random effect for both intercept and slope. The coefficient

of log(RR) for each subject, $b_i = b1_i + b3_i \times gender_i$, will then be used to calculate QTcS for each subject as follows: QTcS = QT/RRbi.

2. An optimized HR-corrected QT interval (QTcI) will be derived from a broader range of HRs by using all QT/RR data on Day 1 of the placebo period. The QT/RR pairs from each subject will be used for that subject's individual correction coefficient, which will be derived from a linear regression model: log(QT) = log(a) + b×log(RR). The coefficient of log(RR) for each subject, bi, will then be used to calculate QTcI for that subject as follows: QTcI = QT/RRbi.

For QTcS and QTcI, the individual correction coefficients, bi, will be listed and also summarized in a table using arithmetic mean, SE, number of subjects, and 90% CI (based on t-distribution).

The method that removes the HR dependence of the QT interval most efficiently will be chosen as primary correction method.

8.3.3. Evaluation for QT-RR Correction Methods

In case a substantial HR effect is observed, defined as a largest ΔΔHR greater than 10 bpm, the relationship between QTc (QTcF and, if derived, QTcS [individual], and QTcI [optimized]) and RR interval will be investigated using on-treatment data (LOXO-305, moxifloxacin, and placebo) by a linear regression model: QTc = c + d x RR. Mean QTc and RR values from all nominal time points (including predose) will be used. The RR coefficient for each subject, d_i, will then be used to calculate the average sum of squared slopes (SSS) for each of the different QT/RR correction methods. The correction method that results in the average on-treatment slope closest to 0 (the smallest average SSS, as described by Tornøe et al 2011[17]) for LOXO-305 and placebo will be deemed the most appropriate HR correction method. If different methods show similar SSS values on placebo as on LOXO-305, priority in the choice will be given to the placebo results. In addition, a scatter plot and quantile plot of QTc (QTcF, QTcS, and QTcI) and RR intervals by treatment with regression line and a linear mixed-effects line (90% CI), respectively, will also be given.

8.3.4. Concentration-QTc Analysis (Primary Analysis)

The relationship between LOXO-305 plasma concentrations and change from baseline QTc (ΔQTcF or ΔQTc corrected with the HR correction method chosen as primary if a substantial HR effect is observed) will be quantified using a linear mixed-effects modeling approach. The model will include ΔQTc as the dependent variable, LOXO-305 plasma concentrations as the explanatory variate (0 for placebo), centered baseline QTc (ie, baseline QTcF for individual subject minus the population mean baseline QTc for all subjects in the same treatment period) as an additional covariate, treatment (active = 1 or placebo = 0) and time (ie, nominal postdose timepoint) as fixed effects, and random effects on the intercept and slope per subject.[18] In addition, if there are significant concentrations of LOXO-305 metabolites, their concentrations/QTc relationship may be explored (exploratory metabolite profiling has shown that unchanged LOXO-305 is the major drug-related component in human plasma).

The degrees of freedom of estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for LOXO-305 concentrations) and the treatment effect-specific intercept (defined as the difference between active and placebo)

will be estimated together with the 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

The geometric mean of the individual C_{max} values for subjects in the active dose group will be determined. The predicted effect and its 2-sided 90% CI for ΔΔQTc (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} of LOXO-305 will be obtained. If the upper bound of the 2-sided 90% CI of the predicted effect of ΔΔQTc at clinically relevant plasma levels of LOXO-305 is below 10 msec, it will be concluded that LOXO-305 does not cause clinically relevant QTc prolongation within the observed plasma concentration ranges.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTc values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTc_{i,k}$ ($\Delta\Delta QTc_{i,k}$) values equal the observed individual $\Delta QTc_{i,k}$ for subject 'i' administered with active drug or placebo at timepoint 'k' minus the estimated population mean placebo effect at timepoint k (ie, time effect). A quantile plot, ie, plot of the quantiles (deciles) of observed drug concentrations and the mean placebo-adjusted ΔQTc (ΔΔQTc) and 90% CI at the median concentration within each decile, will be given. The regression line presenting the model-predicted ΔΔQTc (as described by Tornøe et al[17]) will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. Additional exploratory analysis (via graphical displays and/or model fitting) will include assessing for a delayed effect (hysteresis) and the justification for the choice of the pharmacodynamic model (linear versus nonlinear).

8.3.4.1. Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTc at each postdose timepoint from the by-timepoint analysis and the mean concentrations of LOXO-305 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTc from the by-timepoint analysis and the mean concentrations. If a QT effect > 10 msec (ie, the largest LS mean ΔΔQTc > 10 msec) cannot be excluded in the by-timepoint analysis, and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTc) and peak plasma concentrations (t_{max}) is larger than 1 hour, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if the curve of the hysteresis plot shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

8.3.4.2. Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile (Q-Q) plots for the standardized residuals and the random effects; scatter plots of standardized residuals versus concentration, fitted values, and centered baseline QTc; and box plots of standardized residuals versus nominal time and active treatment will be produced, in addition to the quantile plot described above. Among these plots, the scatter plots of standardized residuals versus concentration and versus centered baseline QTc will also include the locally weighted scatter plot smoothing[19] lines with optimal smoothing parameters selected by the Akaike information criterion with a correction[20]. A scatter plot of observed concentration and ΔQTc

with a locally weighted scatterplot smoothing (LOWESS) line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, specifically an E_{max} model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

8.3.5. Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (ΔQTc) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect of ΔΔQTc is above 5 msec at the geometric mean C_{max} for moxifloxacin, assay sensitivity will be deemed to have been demonstrated.

8.3.6. By-timepoint Analysis (Secondary Analysis)

The analysis for QTc will be based on a linear mixed-effects model with ΔQTc (ΔQTcF, or ΔQTc corrected per the HR correction method chosen as primary if a substantial HR effect is observed) as the dependent variable, period, sequence, time (ie, nominal postdose timepoint), treatment (LOXO-305, moxifloxacin and placebo), and time-by-treatment interaction as fixed effects, and baseline QTc as a covariate. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints for subject within treatment period. If the model with unstructured covariance matrix fails to converge, other covariance matrix such as compound symmetry and autoregressive will be considered. The model will also include a subject-specific random effect. If the fixed effects for period and/or sequence should prove to be nonsignificant (that is, if the p-value > 0.1), these effects may be removed from the model and the analysis will be repeated without those covariates. From this analysis, the LS mean, SE, and 2-sided 90% CI will be calculated for the contrast "LOXO-305 versus placebo" at each postdose timepoint, separately.

For HR, PR, QRS, and QTc intervals with the methods not selected as primary, the analysis will be based on the change from baseline post-dosing values (ΔHR, ΔPR, ΔQRS, and ΔQTc). The same (by-timepoint analysis) model will be used as described above for QTc. The LS mean, SE, and 2-sided 90% CI from the statistical modeling for both change from baseline and placebo-corrected change from baseline values will be listed in the tables and graphically displayed.

8.3.7. Categorical Analysis

The analysis results for categorical outliers will be based on treatment-emergent events (ie, new findings compared to baseline); T-wave morphology and presence of U-waves will be summarized in frequency tables with counts percentages for both number of subjects and number of timepoints. For categorical outliers, the number (percentage) of subjects as well as time points who had increases in absolute treatment-emergent QTc (QTcF, and QTcS and QTcI if derived) values > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, or > 500 msec, and changes from predose baseline of > 30 and ≤ 60 msec, or > 60 msec; increase in PR from predose baseline > 25% to a PR> 200 msec; increase in QRS from predose baseline > 25% to a QRS > 120 msec; decrease in HR from predose baseline > 25% to a HR < 50 bpm; and increase in HR from predose baseline > 25% to a HR > 100 bpm will be determined. For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, ie,

changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicates at the timepoint.

8.4. Pharmacokinetic Analysis

Blood samples for the analysis of concentrations of LOXO-305 in plasma will be collected for 96 hours after administration of LOXO-305 (Treatment A) and LOXO-305 matched placebo (Treatment B). Blood samples for the analysis of concentrations of moxifloxacin in plasma will be collected for CCI (Treatment C).

Blood samples from Treatment A will be analyzed for concentrations of LOXO-305 in plasma through 96 hours after administration of LOXO-305. Blood samples from Treatment B will be analyzed for concentrations of LOXO-305 in plasma only at the single timepoint taken 2 hours after administration of LOXO-305 matched placebo. Blood samples from Treatment C will be analyzed for concentrations of moxifloxacin in plasma through CCI .

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

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

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

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

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

8.4.1. Descriptive Analysis

Plasma concentrations and PK parameters will be summarized with descriptive statistics (number, arithmetic mean, SD, 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. No formal statistical analysis is planned other than previously mentioned.

8.5. Safety Analysis

All safety assessments, including AEs, SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and standard safety 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 on Days 1, 12, and 23. No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

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

8.6. Data Handling and Record Keeping

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

The Data Management Plan will be approved by the Sponsor.

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

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

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

8.7. Quality Control and Quality Assurance

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

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

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

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

9.2. Site Initiation Visit/Investigator Meeting

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

9.3. Disclosure

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

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

9.4. Monitoring

The Sponsor will designate a Study Monitor 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 (or may perform activities remotely as per the Monitoring Plan for this study) and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor 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), and Investigational New Drug Application (21 CFR 312), as appropriate. As such, these sections of US Title 21 CFR, along with the

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

9.9. Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

10. REFERENCES

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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 significant adverse changes in laboratory parameters observed in a subject during a clinical study

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

Categorization of Adverse Events

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

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

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

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

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

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

Pregnancy

As information is available, a pregnancy (including pregnancy in female partners of male subjects) diagnosed through End of Study (EOS) or Early Termination (ET; if the subject discontinues from the study and does not complete a follow-up phone call) and for up to 90 days after study drug administration on Day 23 (or last administration of study drug if subject terminates from the study early) should be reported by the Investigator (or designee) via email to Covance or the Sponsor's Clinical Safety Representative within 24 hours of being notified. Covance or the Sponsor's Clinical Safety Representative will then forward the Pregnancy Form to the Investigator (or designee) for completion.

email: SAEIntake@Covance.com

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and ET study procedures will be performed. The subject or partner should be followed by the Investigator (or designee) until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator (or designee) should notify Covance or the Sponsor's Clinical Safety Representative. At the completion of the pregnancy, the Investigator (or designee) will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (SAE; ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator (or designee) should follow the procedures for reporting an SAE.

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

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

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

Definition of Serious Adverse Events

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

- Death
- A life-threatening adverse drug experience (ie, one that places the subject, in the view of the Investigator [or designee], at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An important medical event that may require medical or surgical intervention to prevent 1 of the above outcomes

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Unexpected Adverse Drug Reaction

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

Reporting

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

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

email: SAEIntake@Covance.com

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

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

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

Appendix 2: Clinical Laboratory Evaluations

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

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 32 for End of Treatment (EOT) or Early Termination (ET) only.
d. Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
e. Urine or breath test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject:

Assessment	Approximate Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Approximate Total Volume (mL)
Serology	8.0	1	8.0
Hemoglobin A1c (HbA1c)	4.0	1	4.0
Pharmacokinetic and/or future exploratory and/or exploratory analysis sampling	6.0 (Treatments A and B)[b]	34	204.0
	4.0 (Treatment C)	14	56.0
Clinical laboratory evaluations: Hematology Clinical chemistry[a] Coagulation	 4.0 4.0 3.0	11	121.0
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:	**409.0 mL**

[a] Thyroid stimulating hormone (TSH) and estimated glomerular filtration rate (eGFR) will be assessed as part of the clinical chemistry sample.
[b] Blood samples collected for analysis of study drug in plasma for Treatments A and B and blood samples for future potential and/or exploratory analysis for Treatments A and B may be collected from the same blood collection vial.

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

Appendix 4: Schedule of Assessments

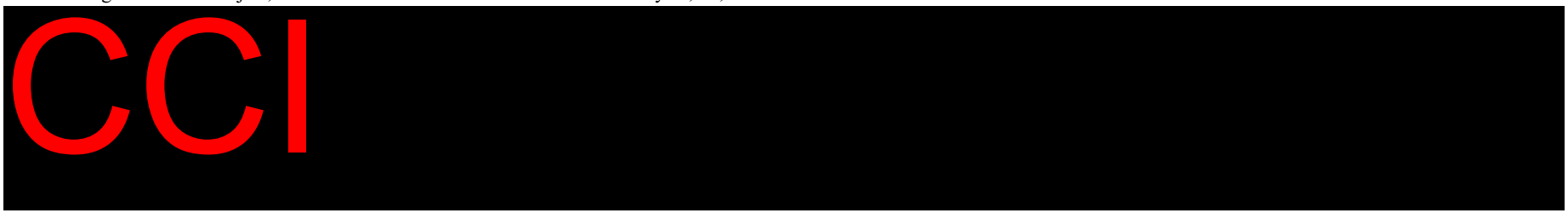
Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Study Conduct: Treatment Period 1 — Study Day 1	2	3	4	5	6	7	8	9	10	11	Treatment Period 2 — Study Day 12	13	14	15	16	17	18	19	20	21	22	Treatment Period 3 — Study Day 23	24	25	26	27	28	29	30	31	32	Clinic Discharge/ EOT/ET[u] — 33	Follow-up Phone Call (EOS) — 7 (± 2) days post EOT/ ET[v]
Confined to the CRU		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	
Standard Safety 12-lead ECG[e]	X	X	X	X	X	X	X						X	X	X	X	X	X						X	X	X	X	X	X						X	
Vital Signs[f,g,h]	X	X	X	X			X						X	X	X			X						X	X	X			X						X	
HDYF? Inquiry[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration			X[k]											X[k]											X[k]											
CCI																																				

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Study Conduct: Treatment Period 1 — Study Day 1	2	3	4	5	6	7	8	9	10	11	Treatment Period 2 — Study Day 12	13	14	15	16	17	18	19	20	21	22	Treatment Period 3 — Study Day 23	24	25	26	27	28	29	30	31	32	Clinic Discharge/ EOT/ET[u] — 33	Follow-up Phone Call (EOS) — 7 (± 2) days post EOT/ ET[v]
CCI																																				
Cardiodynamic Sampling (Holter Monitoring)[m, n]			X	X										X	X										X	X										
Clinical Laboratory Evaluations[o]	X	X		X				X				X			X				X				X			X				X				X	X	
eGFR	X	X																																			
Hepatitis and HIV Screen	X																																			
COVID-19 Testing[p]	X	X																																		
HbA1c Test	X																																			
Drug Screen[q]	X	X																																		
Prior and Concomitant Medications[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[s]	X	X																																	X	X	
FSH Test[t]	X																																			
TSH Test	X																																			

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

a. For details on study procedures, see Section 7.

b. Interim medical history only.

c. Height collected at Screening only; BMI calculated based on Screening height.
d. A complete physical examination will be performed at Check-in (Day -1). An abbreviated physical examination will be performed at EOT (Day 33) or at ET.
e. Standard safety 12-lead ECGs will be obtained at Screening and Check-in (Day -1), and at the following times related to administration of each treatment on Days 1, 12, and 23: predose, and 1, 2, 4, 6, 24, 48, 72, 96, and 240 hours postdose (for Treatment Period 3, 240 hours postdose is EOT [Day 33] or ET). Standard safety 12-lead ECGs will be collected after the subject has rested in the supine position for at least 10 minutes. When scheduled at the same time as PK blood draws, standard safety 12-lead ECGs will be obtained prior to and as close as possible to having blood drawn. The allowed sampling window for standard safety 12-lead ECGs is ± 30 minutes from the nominal timepoint for all postdose standard safety 12-lead ECGs and no less than 10 minutes prior to dosing for predose standard safety 12-lead ECGs.
f. Vital sign measurements (supine BP and pulse rate) will be obtained at Screening, Check-in (Day -1), and at the following times related to administration of each treatment on Days 1, 12, and 23: predose, and 1, 4, 8, 12, 24, 96, and 240 hours postdose (for Treatment Period 3, 240 hours postdose is EOT [Day 33] or ET). Blood pressure and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes. When scheduled at the same time as PK blood draws, vital sign measurements should be carried out prior to and as close as possible to having blood drawn. The allowed sampling window for vital sign measurements is ± 30 minutes from the nominal timepoint for all postdose vital sign measurements and no less than 10 minutes prior to dosing for predose vital sign measurements.
g. Respiratory rate and body temperature will be obtained at Screening, Check-in (Day -1), predose on Days 1, 12, and 23, and at EOT (Day 33) or ET.
h. Oxygen saturation will be measured via pulse oximetry at Screening, Check-in (Day -1), predose on Days 1, 12, and 23, and at EOT (Day 33, 240 hours postdose on Day 23) or ET. The allowed sampling window for oxygen saturation measurements is ± 30 minutes from the nominal timepoint for all postdose oxygen saturation measurements and no less than 10 minutes prior to dosing for predose oxygen saturation measurements.
i. A HDYF? inquiry will be performed at Screening (after the ICF is signed), at Check-in (Day -1), at each postdose vital sign measurement, and at an appropriate time for all other days.
j. Adverse events and SAEs will be collected beginning at informed consent. Adverse events will be recorded throughout the study (ie, from signing of the ICF until EOS, or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed by the Investigator [or designee]) as related to study procedures, or if the event occurs after study drug administration on Day 1 through EOT or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug are to be recorded. All SAEs that develop from the time of ICF signing until EOS (or ET if the subject discontinues from the study and does not complete a follow-up phone call) are to be reported.
k. Treatment A (900 mg LOXO-305), Treatment B (placebo to match 900 mg LOXO-305), and Treatment C (400 mg moxifloxacin) will be administered in accordance with the randomization scheme assigned to each subject, with each treatment administered on either Days 1, 12, or 23.
l. 

m. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli (ie, TV, loud radio, interactions with other subjects, etc.) for at least 10 minutes before and 5 minutes during the cardiodynamic ECG extraction. Subjects will remain lying down or sitting and awake for the first 7 hours of the 24-hour postdose cardiodynamic ECG monitoring period. Holter monitors will be placed on subjects approximately 1.5 hours prior to dosing.
n. Cardiodynamic sampling (Holter monitor ECG extraction) will be collected at the following times related to dosing: 45, 30, and 15 minutes predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8.5, 12, and 24 hours postdose. A light meal will be provided immediately following completion of the cardiodynamic ECG recording at the 6-hour timepoint and a full meal will be provided immediately after the 12-hour postdose timepoints. A snack can also be given just after the 8.5-hour postdose timepoint. Meals and snacks must be scheduled to be completed at least

90 minutes prior to any scheduled ECG (ie, standard safety 12-lead ECG, or cardiodynamic ECG). The allowed sampling window for cardiodynamic ECGs will be the following: within 30 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints within the first 24 hours postdose.

o. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and UA will be performed at Screening, Check-in (Day -1), Day 2 (24 hours postdose on Day 1), Day 6 (120 hours postdose on Day 1), Day 10 (216 hours postdose on Day 1), Day 13 (24 hours postdose on Day 12), Day 17 (120 hours postdose on Day 12), Day 21 (216 hours postdose on Day 12), Day 24 (24 hours postdose on Day 23), Day 28 (120 hours postdose on Day 23), and Day 32 (216 hours postdose on Day 23), if the subject completes the study (EOT) or on the day of ET. At ET or the day before EOT (Day 32), subjects are not required to be fasted prior to clinical laboratory evaluations.
p. Testing for COVID-19 will be conducted at a minimum at Screening and Check-in (Day -1). Testing for COVID-19 may also be conducted periodically during the subject's CRU confinement, at the discretion of the Investigator (or designee). Tests will be performed by rapid polymerase chain reaction or equivalent.
q. Urine drug screen for drugs of abuse (including cotinine) and alcohol screen (urine or breath).
r. Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved prescription and over-the-counter medications taken by a subject within 14 days or 5 half-lives (if known), whichever is longer, prior to Day 1 will be recorded on the subject's electronic CRF.
s. Female subjects only. Performed at Screening, Check-in (Day -1), and Day 32 (216 hours postdose on Day 23), if the subject completes the study (EOT) or on the day of ET.
t. Post-menopausal female subjects only.
u. End of Treatment is defined as when the subject is released from the CRU following completion of all assessments through EOT (Day 33). Early Termination is defined as when the subject is released from the CRU if the subject terminates the study early. Vital sign measurements, standard safety ECG, and abbreviated physical examination results are to be available for review by the Investigator (or designee) prior to subject release from the CRU on Day 33 (EOT) or ET. Clinical laboratory results (for clinical chemistry, hematology, coagulation, and UA) and serum pregnancy test results (female subjects only) are to be available for review by the Investigator (or designee) prior to subject release from the CRU at the EOT visit and prior to subject release from the CRU at the ET visit, if available.
v. To be conducted 7 days (± 2 days) following EOT (Day 33) or ET. End of Study is defined as when the subject is contacted by the CRU for a follow-up phone call 7 days (± 2 days) after the EOT visit or ET visit to determine if any SAE or study drug-related AE has occurred since the EOT or ET visit. All subjects who received study drug (including subjects who are terminated early) will receive a follow-up phone call.