Protocol: LOXO-BTK-20007 (Final version 1.0)

A Phase I, Open-label, Two-part Study of the Absorption, Metabolism, Excretion, and the Absolute Bioavailability of [14C]-LOXO-305 in Healthy Male Subjects

NCT06180954

Approval Date: 29-June-2020

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Protocol Status: Final
Protocol Date: 29 June 2020
Protocol Version: 1.0

Investigational Medicinal Product: LOXO-305

Protocol Reference Number: LOXO-BTK-20007
Covance Study Number: 8419667
IND Number: 139876

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SYNOPSIS

Study Title

A Phase I, Open-label, Two-part Study of the Absorption, Metabolism, Excretion, and the Absolute Bioavailability of [^{14}C]-LOXO-305 in Healthy Male Subjects

Objectives

Part 1:

The primary objectives of Part 1 of the study are:

- to determine the mass balance and routes of elimination of [^{14}C]-LOXO-305 following oral administration of a single dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 μCi) in healthy male subjects
- to assess the pharmacokinetics (PK) of LOXO-305 following a single oral dose of [^{14}C]-LOXO-305
- to determine the whole blood and plasma concentrations of total radioactivity following a single oral dose of [^{14}C]-LOXO-305
- to determine urinary and fecal recovery of total radioactivity following a single oral dose of [^{14}C]-LOXO-305
- to characterize and identify metabolites of LOXO-305 in plasma, urine, and feces following a single oral dose of [^{14}C]-LOXO-305.

Part 2:

The primary objectives of Part 2 of the study are:

- to determine the absolute bioavailability of LOXO-305 following a single oral dose of 200 mg LOXO-305 along with an intravenous (IV) dose of < 100 μg of [^{14}C]-LOXO-305 (containing ~1 μCi of radioactivity [microtracer])
- to evaluate the PK of LOXO-305 and [^{14}C]-LOXO-305 following oral dosing of LOXO-305 and IV dosing of [^{14}C]-LOXO-305
- to evaluate the plasma concentration of total radioactivity following IV dosing of [^{14}C]-LOXO-305
- to evaluate the urinary excretion of [^{14}C]-LOXO-305 and total radioactivity following IV dosing of [^{14}C]-LOXO-305
- to evaluate the fecal recovery of [^{14}C]-LOXO-305 and total radioactivity following IV dosing of [^{14}C]-LOXO-305.

Part 1:

The secondary objective of Part 1 of the study is:

- to assess the safety and tolerability of [^{14}C]-LOXO-305 when administered to healthy male subjects.

Part 2:

The secondary objective of Part 2 of the study is:

- to assess the safety and tolerability of LOXO-305 and [^{14}C]-LOXO-305 when administered to healthy male subjects.

Study design

This study will be an open-label, 2-part, absorption, metabolism, excretion (AME) and absolute bioavailability study of [^{14}C]-LOXO-305. Subjects in Part 1 will not participate in Part 2, nor will subjects in Part 2 participate in Part 1. Part 1 and Part 2 are independent of each other and do not need to be conducted in sequential order.

Part 1 is designed to evaluate the AME profiles of LOXO-305, to identify and characterize metabolites of LOXO-305, and to assess the safety and tolerability of [^{14}C]-LOXO-305. Subjects in Part 1 will be administered a single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 μCi) as an oral solution.

Part 2 is designed to determine the absolute bioavailability of LOXO-305, to evaluate the plasma concentration of total radioactivity, to evaluate the urinary excretion of [^{14}C]-LOXO-305 and total radioactivity, to evaluate the fecal excretion of [^{14}C]-LOXO-305 and total radioactivity, and to assess the safety and tolerability of LOXO-305 and [^{14}C]-LOXO-305. Subjects in Part 2 will be administered 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.

Six subjects will participate in each part of the study, such that a total of 12 subjects will be evaluated in the study. Each subject will participate in either Part 1 or Part 2, but not both. In the event of early withdrawal of any subjects and/or in order to ensure 6 subjects complete each part of the study, replacement subjects may be enrolled at the discretion of the Sponsor.

The start of the study is defined as the earliest date a subject who is enrolled in either part of the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned a dose of study drug; this definition excludes screen failure subjects. A subject who completes sufficient total radioactivity recovery and metabolite sample collection (Part 1 only), or LOXO-305 and [^{14}C]-LOXO-305 (Part 2 only) sampling prior to Clinic Discharge is considered to have completed the study. The end of the study is defined as the latest date a subject receives the Follow-up Call. The planned duration of study conduct for Part 1 is up to 60 days from Screening through the Follow-up Call. The planned duration of study conduct for Part 2 is up to 47 days from Screening through the Follow-up Call.

Part 1:

After a Screening period of up to 28 days, subjects will check in to the Clinical Research Unit (CRU) on Day -1 to confirm eligibility and to become familiar with study procedures. On the morning of Day 1, following an overnight fast of at least 10 hours, subjects will receive a single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) administered as an oral solution. Subjects will be confined at the CRU from the time of Check-in (Day -1) until Clinic Discharge (between Days 12 and 22). After completing discharge procedures, subjects will be discharged from the CRU as early as Day 12 and up to Day 22, provided recovery of radioactivity has reached the following threshold values:

- Plasma radioactivity below the limit of quantification for 2 consecutive collections, and
- ≥ 90% of the radioactive dose is recovered, and
- ≤ 1% of the radioactive dose per day is recovered in excreta (urine and feces) for 3 consecutive days on which a fecal sample is collected.

Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator (or designee). Subjects will receive a Safety Follow-up Call approximately 7 days after Clinic Discharge.

Samples for determination of LOXO-305 concentrations in plasma, total radioactivity concentrations in plasma, whole blood, urine, and feces, and for metabolite profiling/characterization will be obtained through at least 264 hours postdose (Day 12), and possibly up to 504 hours postdose (Day 22).

Part 2:

After a Screening period of up to 28 days, subjects will check in to the CRU on Day -1 to confirm eligibility and to become familiar with study procedures. On the morning of Day 1, following an overnight fast of at least 10 hours, subjects will receive a single oral dose of 200 mg of LOXO-305 as 2 × 100-mg tablets and 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. Subjects will be confined at the CRU from the time of Check-in (Day -1) until Day 9 and will be discharged from the CRU after completing all discharge procedures. Subjects will receive a Follow-up Call approximately 7 days after Clinic Discharge.

Samples for determination of LOXO-305 in plasma, and [^{14}C]-LOXO-305 and total radioactivity concentrations in plasma, urine, and feces will be obtained through 192 hours postdose (Day 9).

Both Parts:

In this study, physical examinations, 12-lead electrocardiograms (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 AEs (SAEs) will be collected beginning at informed consent. Adverse events will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until Early Termination [ET] if the subject discontinues from the study and does not complete a Follow-up Phone Call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through End of Treatment [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

Six subjects will participate in each part of the study. Each subject will participate in either Part 1 or Part 2, but not both.

In Parts 1 and 2, in the event of early withdrawal of any subjects, and/or to ensure 6 subjects complete each part of the study, replacement subjects may be enrolled at the discretion of the Sponsor.

Diagnosis and main criteria for inclusion

Healthy male subjects between 18 and 55 years of age, inclusive, with a body mass index of 18.5 to 32.0 kg/m^2, inclusive, at Screening. Subjects will be in good general health, based on medical history, physical examination findings, vital sign measurements, 12-lead ECG, or clinical laboratory evaluations at Screening and/or Check-in (Day -1), as determined by the Investigator (or designee).

Investigational medicinal products, dose, and mode of administration

Part 1: Subjects will receive a single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) as an oral solution following an overnight fast of at least 10 hours.

Part 2: Following an overnight fast of at least 10 hours, subjects will receive a single oral dose of 200 mg of 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 radioactivity [microtracer]) administered as an IV push over approximately 2 minutes.

Duration of subject participation in the study

Planned Enrollment/Screening Duration:

- Part 1; approximately 28 days (Days -29 to -2).

- Part 2; approximately 28 days (Days -29 to -2).

Length of CRU Confinement:

- Part 1; up to 23 days (Days -1 to 22).
- Part 2; 10 days (Days -1 to 9).

Planned Study Conduct Duration:

- Part 1; up to 60 days (Screening to Safety Follow-up Call).
- Part 2; up to 47 days (Screening to Safety Follow-up Call).

Endpoints

Pharmacokinetics:

Part 1:

Whenever possible, the following PK parameters will be calculated based on the plasma concentrations of LOXO-305 and on plasma and whole blood concentrations of total radioactivity: maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), area under the concentration-time curve (AUC) from hour 0 to the last measurable concentration (AUC_{0-t}), AUC from time 0 extrapolated to infinity (AUC_{0-inf}), apparent terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL/F; for LOXO-305 only), apparent volume of distribution during the terminal phase (V_z/F; for LOXO-305 only), AUC_{0-inf} of total radioactivity in whole blood/AUC_{0-inf} of total radioactivity in plasma (Blood/Plasma AUC Ratio), and AUC_{0-inf} of LOXO-305 in plasma/AUC_{0-inf} of total radioactivity in plasma (Plasma LOXO-305/Total Radioactivity AUC Ratio).

Whenever possible, the following PK parameters will be calculated based on the urine concentrations of total radioactivity: amount excreted in urine per sampling interval (A_{eu}), cumulative amount excreted in urine (cumulative A_{eu}), percentage of dose excreted in urine per sampling interval (f_{eu}), and cumulative percentage of dose excreted in urine (cumulative f_{eu}).

Whenever possible, the following PK parameters will be calculated based on the fecal concentrations of total radioactivity: amount excreted in feces per sampling interval (A_{ef}), cumulative amount excreted in feces (cumulative A_{ef}), percentage of dose excreted in feces per sampling interval (f_{ef}), and cumulative percentage of dose excreted in feces (cumulative f_{ef}).

In Part 1, the PK parameters for relevant metabolites of LOXO-305 may be calculated, as deemed appropriate, based on plasma, urine, and fecal concentration levels.

Part 2:

Following oral dosing of LOXO-305, whenever possible, the following PK parameters will be calculated based on the plasma concentrations of LOXO-305 and total radioactivity: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, apparent terminal elimination rate constant (λ_z), $t_{1/2}$, absolute

bioavailability (F; for LOXO-305 only), CL/F (for LOXO-305 only), and V_z/F (for LOXO-305 only).

Following IV microtracer dosing of [^{14}C]-LOXO-305 (containing ~1 μCi of radioactivity), whenever possible, the following PK parameters will be calculated based on the plasma concentrations of [^{14}C]-LOXO-305: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, total clearance (CL), volume of distribution during the terminal phase (V_z), and volume of distribution at steady state (V_{ss}).

Whenever possible, the following PK parameters will be calculated for each subject based on the urine concentrations of [^{14}C]-LOXO-305 and total radioactivity following IV dosing of [^{14}C]-LOXO-305: A_{eu}, cumulative A_{eu}, renal clearance (CL_R; [^{14}C]-LOXO-305 only), f_{eu}, and cumulative f_{eu}.

Whenever possible, the following PK parameters will be calculated for each subject based on the fecal concentrations of [^{14}C]-LOXO-305 and total radioactivity following IV dosing of [^{14}C]-LOXO-305: A_{ef}, cumulative A_{ef}, f_{ef}, and cumulative f_{ef}.

Safety:

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

Statistical methods

For Parts 1 and 2, descriptive statistics (number of observations, arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric coefficient of variation) will be calculated for the PK parameters. No formal statistical PK analyses are planned. For Parts 1 and 2, descriptive statistics will be calculated on the safety parameters. No formal statistical safety analyses are planned.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ADL	Activities of Daily Living
A_{ef}	amount excreted in feces
A_{eu}	amount excreted in urine
ALARA	as low as (is) reasonably achievable
AME	absorption, metabolism, and excretion
AMS	accelerator mass spectrometry
API	active pharmaceutical ingredient
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}inf}$ Blood/ Plasma Ratio	area under the concentration-time curve from time 0 extrapolated to infinity of whole blood total radioactivity to area under the concentration-time curve from time 0 extrapolated to infinity of plasma total radioactivity
$AUC_{0\text{-}inf}$ Plasma LOXO-305/Total Radioactivity Ratio	area under the concentration-time curve from time 0 extrapolated to infinity of plasma LOXO-305 relative to area under the concentration-time curve from time 0 extrapolated to infinity of plasma total radioactivity
$AUC_{0\text{-}t}$	area under the concentration-time curve from hour 0 to the last measurable concentration
AV	atrioventricular
BID	twice daily
BMI	body mass index
BP	blood pressure
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	total clearance
CL/F	apparent systemic clearance
CLL	chronic lymphocytic leukemia
CL_R	renal clearance
C_{max}	maximum observed concentration
COVID-19	SARS-CoV-2
CRU	Clinical Research Unit
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CV	coefficient of variation

CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
F	absolute bioavailability
FDA	Food and Drug Administration
f_{ef}	percentage of dose excreted in feces
f_{eu}	percentage of dose excreted in urine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing 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
IB	Investigator's Brochure
IC_{90}	concentration required for 90% inhibition
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LSC	liquid scintillation counting
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NHL	non-Hodgkin lymphoma
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
RSI	Reference Safety Information
SAE	serious adverse event

SAP	Statistical Analysis Plan
SDD	spray-dried dispersion
SLL	small lymphocytic lymphoma
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
t_{max}	time to maximum observed concentration
TSH	thyroid-stimulating hormone
UA	urinalysis
US	United States
V_{ss}	volume of distribution at steady state
Vz	volume of distribution
V_z/F	apparent volume of distribution

1. INTRODUCTION

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

1.1. Background

LOXO-305 (also known as LY3527727) is a selective inhibitor of the Bruton's tyrosine kinase (BTK) being developed by Loxo Oncology. LOXO-305 is distinct from the approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) in several important ways including on the basis of its selectivity, favorable ADME properties, and non-covalent binding mode.[2] These features enable LOXO-305 to achieve pharmacokinetic (PK) exposures that exceed the BTK concentration required for 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, with more than 300-fold more selective for BTK versus 370 other kinases tested and no significant inhibition of non-kinase off-targets at 1 μM, thus limiting the potential for off-target mediated toxicities. Collectively, these unique properties of LOXO-305 are expected to deliver more potent, continuous, and selective inhibition of BTK in a variety of settings, potentially resulting in increased efficacy. Of note, the activity of LOXO-305 in diverse preclinical model systems supports this underlying hypothesis.[2]

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

1.2. Non-clinical Pharmacokinetics

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

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

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

LOXO-305 was metabolized slowly by human microsomal fractions and hepatocytes. The low rates of metabolism in both these human in vitro systems suggest that LOXO-305 will have low clearance in humans. In vitro data with cloned expressed cytochrome P450 (CYP)

enzymes and human liver microsomes indicate that CYP3A4 is the primary CYP enzyme that metabolizes LOXO-305. It is also a substrate for direct glucuronidation.

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

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

In a Good Laboratory Practice (GLP) in vitro assay for human ether-à-go-go-related gene (hERG) activity, the concentration resulting in 50% inhibition for the inhibitory effects of LOXO-305 on hERG potassium currents was 32 μM, which is approximately 50-fold 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 dog. The C_{max} for this dose was 10000 ng/mL, which is approximately 1.6-fold above the predicted C_{max} plasma LOXO-305 concentration (6430 ng/mL) at the proposed clinical starting dose of 200 mg QD. Furthermore, there were no LOXO-305-related abnormalities in rhythm or waveform morphology in the GLP 28-day repeated-dose toxicity study in dogs at the low and mid-dose groups based on comparison of predose and postdose ECG recordings. The high dose (90/60 mg/kg/dose twice daily [BID]) was not evaluated as animals in this group were moribund/debilitated and were terminated on Day 13. Mean QTc interval was statistically significantly prolonged (+6%; +15 msec) on Day 26 of the dosing phase in males administered 30/10 mg/kg/dose BID compared with controls. The prolongation in QTc 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 30/10 mg/kg/dose BID.

1.3. Summary of Clinical Experience

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

As of 09 April 2020, safety data were available from 172 treated patients, with 300 mg QD as the highest dose administered (Section 1.3.1). As of 30 March 2020 (data cutoff date), PK data were available from 107 patients (Section 1.3.2).

1.3.1. Safety

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

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

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

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

1.3.2. Pharmacokinetics

As of 30 March 2020, PK data were available from 107 patients enrolled in LOXO-BTK-18001. Steady-state PK parameters of LOXO-305 in these cancer patients could be derived from data collected on Cycle 1 Day 8 and are shown in Table 1. These data show that LOXO-305 is absorbed after oral administration with a median time of maximal plasma concentration (T_{max}) of approximately 2 hours and low clearance (Table 1). Due to the limited sampling interval (0-8 hours), imputation for the 24-hour sample was made from the Cycle 1, Day 8 predose sample, leading to an estimated plasma half-life of approximately 20 hours. Following administration of doses of 100 mg QD higher, mean trough plasma levels of LOXO-305 exceeded the concentration required for 90% inhibition (IC_{90} = 825 ng/mL) of BTK in vitro (Figure 1).

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

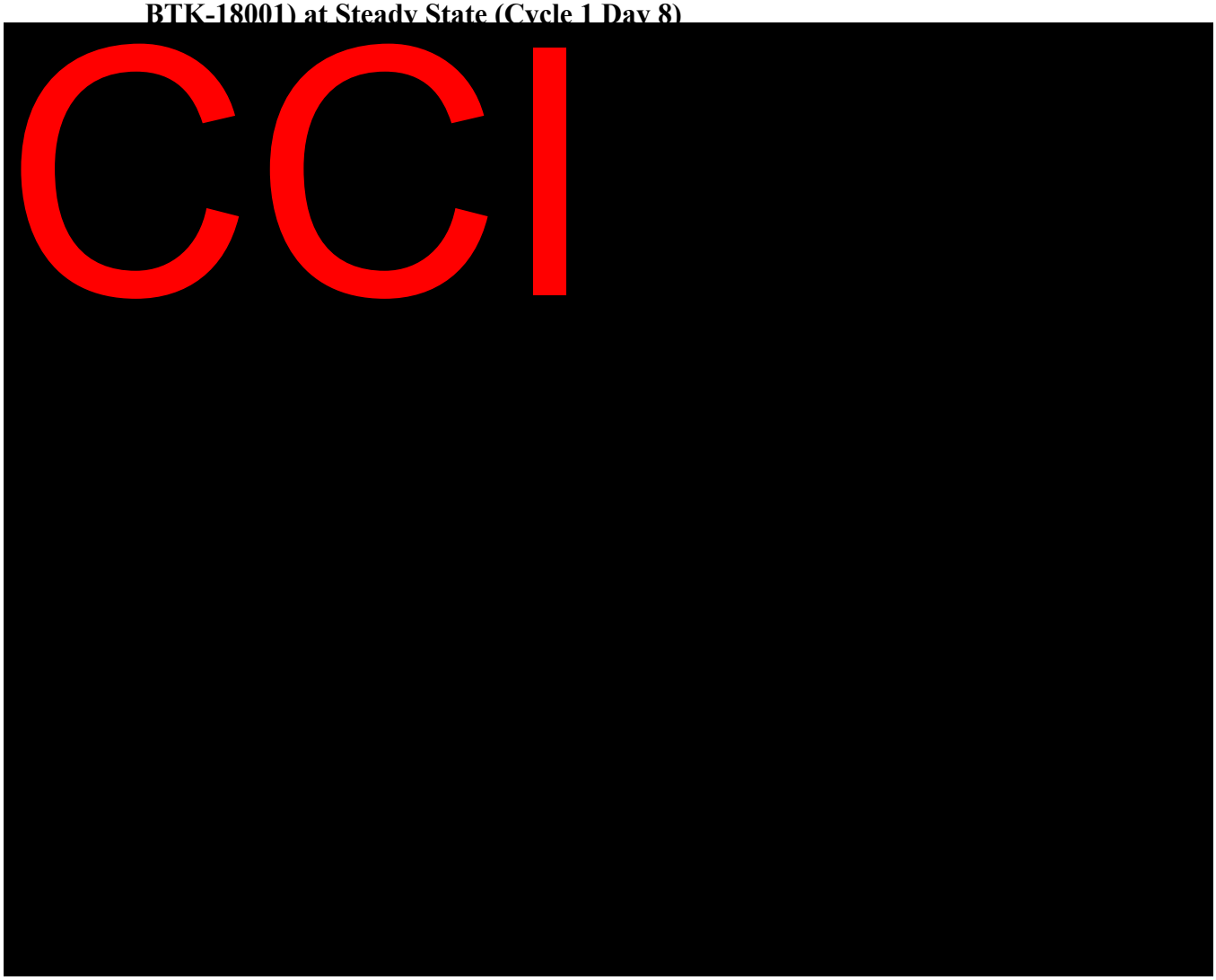
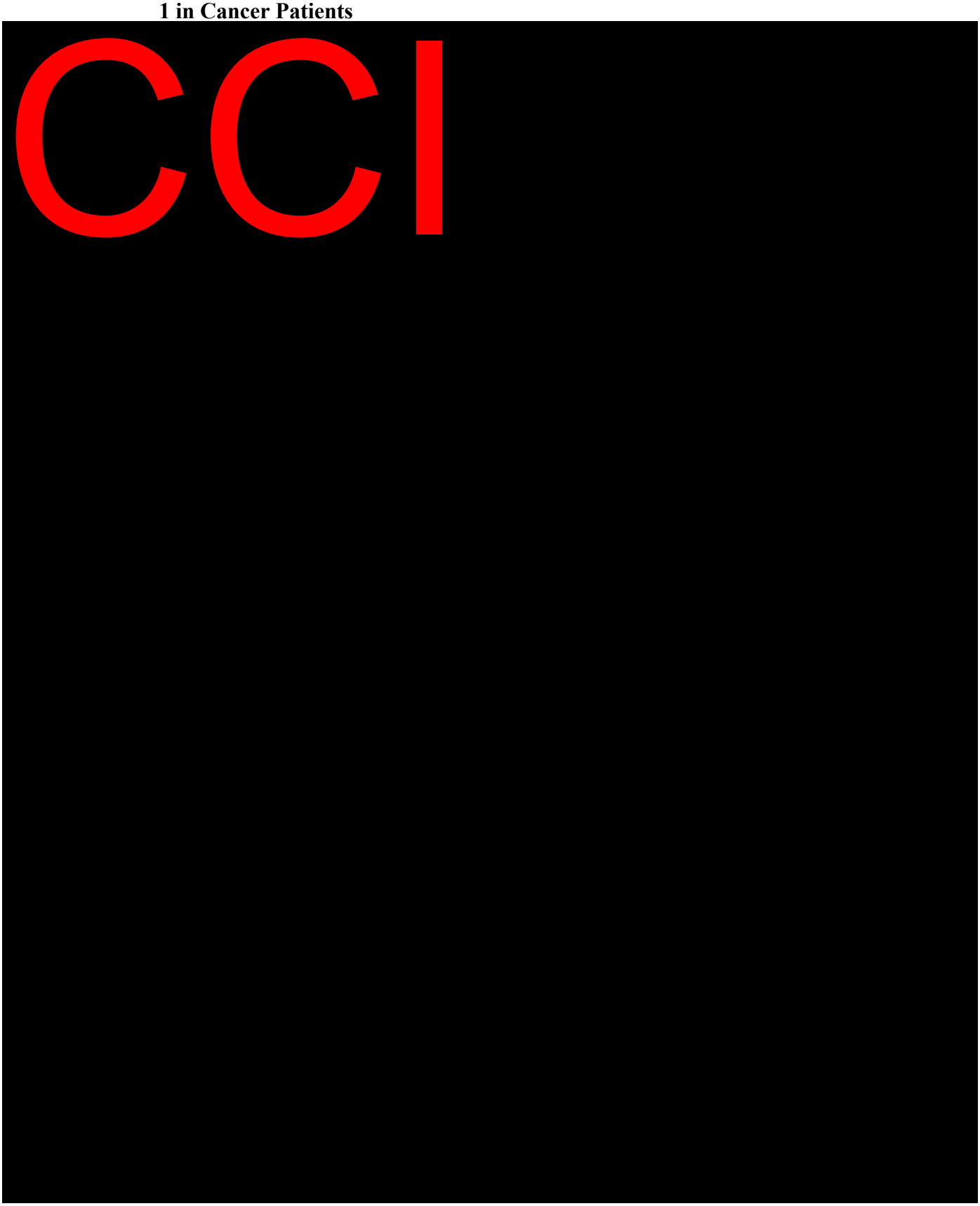


Figure 1 Arithmetic Mean (±SD) Plasma Concentration of LOXO-305 Following Daily Oral Administrations on Day 1 (top panel) and Day 8 (bottom panel) of Cycle 1 in Cancer Patients



1.4. Study Rationale

The purpose of Part 1 of this study is to determine the absorption, metabolism, and excretion (AME) of [^{14}C]-LOXO-305 and to characterize and determine the metabolites present in plasma, urine, and, where possible, feces in healthy male subjects following a single oral administration. Knowledge of the metabolism and excretion of parent drug and its metabolites is useful for evaluating the Metabolites in Safety Testing requirements elucidated in the Food and Drug Administration (FDA) Guidance[9] and International Conference on Harmonisation M3[10] and the likelihood of effects of renal or hepatic impairment on the disposition of LOXO-305 and the likelihood for drug-drug interactions with LOXO-305. The results from this study may guide future study designs using special populations or evaluating the potential for drug-drug interactions.

The purpose of Part 2 of this study is to determine the absolute bioavailability of LOXO-305 in a tablet formulation in humans using an IV microtracer of [^{14}C]-LOXO-305 (containing ~1 µCi radioactivity). Absolute bioavailability information will aid in the planning and design of future studies and may be used to interpret PK data from these studies.

1.5. Risk Assessment

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. The dose of LOXO-305 administered in this study is not anticipated to induce any potential risk to subjects participating in this study as it is a single dose which does not exceed the highest dose safely administered in first-in-human studies.[1] More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with LOXO-305 may be found in the IB.[1]

For Part 1, the planned radioactive dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) is expected to provide a sufficient radioactive signal to achieve the study objectives with minimal radiation risk to subjects. Based on the dosimetry analysis in pigmented rats, the overall whole-body radiation dose in a male subject after administration of a single 100-µCi (3.7-MBq) oral dose of [^{14}C]-LOXO-305 was calculated to be 120 mrem (1.2 mSv) when using allometric conversion.[11] This value is well below the FDA exposure limit of 3000 mrem after a single dose for human isotope studies.[12] Based on the PK and available dosimetry data, administration of a single 200-µCi (7.4-MBq) oral dose of [^{14}C]-LOXO-305 would not be expected to represent a significant radiation exposure risk when administered to healthy male subjects in a clinical trial.

For Part 2, the radioactive dose of ~1 µCi of [^{14}C]-LOXO-305 (microtracer) is only about 0.5% of the radioactive dose planned for Part 1 and will present minimal radiation risk to healthy subjects. The low levels of radioactivity planned for Part 2 will necessitate the use of AMS as a highly sensitive analytical technique for quantifying the radioactivity in plasma, urine, and fecal samples. The radioactive dose of ~1 µCi together with the use of AMS for analysis of radioactivity is expected to allow for completion of study objectives of Part 2 with minimal radiation exposure risk to healthy subjects.

The potential risk of participating in this study is well managed by the study set-up and is considered negligible. The safety monitoring practices employed will include AE reporting, vital sign measurements, 12-lead ECG, clinical laboratory evaluations, and physical examinations, and are considered adequate to protect the subjects' safety.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

Part 1:

The primary objectives of Part 1 of the study are:

- to determine the mass balance and routes of elimination of [^{14}C]-LOXO-305 following oral administration of a single dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 μCi) in healthy male subjects
- to assess the PK of LOXO-305 following a single oral dose of [^{14}C]-LOXO-305
- to determine the whole blood and plasma concentrations of total radioactivity following a single oral dose of [^{14}C]-LOXO-305
- to determine urinary and fecal recovery of total radioactivity following a single oral dose of [^{14}C]-LOXO-305
- to characterize and identify metabolites of LOXO-305 in plasma, urine, and feces following a single oral dose of [^{14}C]-LOXO-305.

Part 2:

The primary objectives of Part 2 of the study are:

- to determine the absolute bioavailability of LOXO-305 following a single oral dose of 200 mg LOXO-305 along with an IV dose of < 100 μg of [^{14}C]-LOXO-305 (containing ~1 μCi of radioactivity [microtracer])
- to evaluate the PK of LOXO-305 and [^{14}C]-LOXO-305 following oral dosing of LOXO-305 and IV dosing of [^{14}C]-LOXO-305
- to evaluate the plasma concentration of total radioactivity following IV dosing of [^{14}C]-LOXO-305
- to evaluate the urinary excretion of [^{14}C]-LOXO-305 and total radioactivity following IV dosing of [^{14}C]-LOXO-305
- to evaluate the fecal recovery of [^{14}C]-LOXO-305 and total radioactivity following IV dosing of [^{14}C]-LOXO-305

2.1.2. Secondary Objectives

Part 1:

The secondary objective of Part 1 of the study is:

- to assess the safety and tolerability of [^{14}C]-LOXO-305 when administered to healthy male subjects.

Part 2:

The secondary objective of Part 2 of the study is:

- to assess the safety and tolerability of LOXO-305 and [^{14}C]-LOXO-305 when administered to healthy male subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

Part 1:

The primary PK endpoints of LOXO-305 in plasma and total radioactivity in whole blood and plasma following oral administration of [^{14}C]-LOXO-305 are as follows:

- area under the concentration-time curve (AUC) from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$)
- AUC from hour 0 to the last measurable concentration ($AUC_{0\text{-}t}$)
- maximum observed concentration (C_{max})
- t_{max}
- apparent terminal elimination half-life ($t_{1/2}$)
- apparent systemic clearance (LOXO-305 only; CL/F)
- apparent volume of distribution (LOXO-305 only; V_z/F)
- $AUC_{0\text{-}inf}$ of plasma LOXO-305 relative to $AUC_{0\text{-}inf}$ of plasma total radioactivity ($AUC_{0\text{-}inf}$ Plasma LOXO-305/Total Radioactivity Ratio)
- $AUC_{0\text{-}inf}$ of whole blood total radioactivity to $AUC_{0\text{-}inf}$ of plasma total radioactivity ($AUC_{0\text{-}inf}$ Blood/Plasma Ratio).

The primary PK endpoints of total radioactivity in urine are as follows:

- amount excreted in urine (A_{eu})
- cumulative A_{eu}
- percentage of dose excreted in urine (f_{eu})
- cumulative f_{eu}.

The primary PK endpoints of total radioactivity in feces are as follows:

- amount excreted in feces (A_{ef})
- cumulative A_{ef}
- percentage of dose excreted in feces (f_{ef})
- cumulative f_{ef}.

The primary outcome for metabolites will be derived:

- metabolic profile of LOXO-305
- identification of LOXO-305 metabolites.

Part 2:

The primary PK endpoints of LOXO-305 and total radioactivity in plasma following oral administration of LOXO-305 are as follows:

- $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, t_{max}, $t_{1/2}$, CL/F (LOXO-305 only), and V_z/F (LOXO-305 only)
- absolute bioavailability (F; LOXO-305 only).

The primary PK endpoints of [^{14}C]-LOXO-305 in plasma following IV administration of [^{14}C]-LOXO-305 are as follows:

- $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, t_{max}, and $t_{1/2}$
- total clearance (CL)
- V_z
- volume of distribution at steady state (V_{ss}).

The primary PK endpoints of [^{14}C]-LOXO-305 and total radioactivity in urine collections are as follows:

- A_{eu}, cumulative A_{eu}, f_{eu}, cumulative f_{eu}
- renal clearance (CL_R; [^{14}C]-LOXO-305 only).

The primary PK endpoints of [^{14}C]-LOXO-305 and total radioactivity in feces collections are as follows:

- A_{ef}, cumulative A_{ef}, f_{ef}, cumulative f_{ef}.

Other PK parameters may also be reported.

2.2.2. Secondary Endpoints

The secondary safety outcome measures for both parts of this study are as follows:

- monitoring AEs

- clinical laboratory evaluations
- 12-lead ECG parameters
- vital sign measurements
- physical examinations.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be an open-label, nonrandomized, 2-part, AME and absolute bioavailability study of [^{14}C]-LOXO-305 in healthy male subjects. Subjects in Part 1 will not participate in Part 2, nor will subjects in Part 2 participate in Part 1. Parts 1 and 2 are independent of each other and do not need to be conducted in sequential order.

Part 1 is designed to evaluate the AME profiles of LOXO-305, to identify and characterize metabolites of LOXO-305, and to assess the safety and tolerability of [^{14}C]-LOXO-305. Subjects in Part 1 will be administered a single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) as an oral solution. Six subjects will participate in each part of the study. Each subject will participate in either Part 1 or Part 2, but not both. In the event of early withdrawal of any subjects and/or to ensure 6 subjects complete each part of the study, replacement subjects may be enrolled at the discretion of the Sponsor.

Part 2 is designed to determine the absolute bioavailability of LOXO-305, to evaluate the plasma concentration of total radioactivity, to evaluate the urinary excretion of [^{14}C]-LOXO-305 and total radioactivity, to evaluate the fecal excretion of [^{14}C]-LOXO-305 and total radioactivity, and to assess the safety and tolerability of LOXO-305 and [^{14}C]-LOXO-305. Subjects in Part 2 will be administered a single oral dose of 200 mg of 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.

Six subjects will participate in each part of the study. Each subject will participate in either Part 1 or Part 2, but not both.

In the event of early withdrawal of any subjects and/or to ensure 6 subjects complete each part of the study, replacement subjects may be enrolled at the discretion of the Sponsor.

The start of the study is defined as the earliest date a subject who is enrolled in either part of the study signs an Informed Consent Form (ICF). A subject who completes sufficient total radioactivity and metabolite (Part 1 only), or LOXO-305 and [^{14}C]-LOXO-305 (Part 2 only) sampling prior to Clinic Discharge is considered to have completed the study. The end of the study is defined as the latest date a subject receives the Follow-up Call. The planned duration of study conduct for Part 1 is up to 60 days from Screening through the Follow-up Call. The planned duration of study conduct for Part 2 is up to 47 days from Screening through the Follow-up Call.

A schematic of the study design of Part 1 is presented in Figure 1 and a schematic of the study design of Part 2 is presented in Figure 2.

Figure 2 Study Design Schematic: Part 1

Screening	Check-in	Dosing[a]	LOXO-305, Total Radioactivity Concentrations, and MetID Sampling	Clinic (CRU) Discharge[b]	Follow-up Call[c]
Days -29 to -2	Day -1	Day 1	Day 1 to Clinic (CRU) Discharge	Days 12 to 22	Approximately 7 days after Clinic (CRU) Discharge
	CRU Confinement				

CRU = Clinical Research Unit; MetID = metabolite profiling and identification
[a] Single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) administered as an oral solution following an overnight fast of at least 10 hours.
[b] Subjects will be discharged from the CRU starting on Day 12 if plasma radioactivity is below the limit of quantification for 2 consecutive collections, and ≥ 90% of the radioactive dose is recovered and ≤ 1% of the radioactive dose per day is recovered in excreta (urine and feces) for 3 consecutive days on which a fecal sample is collected. If these criteria are not satisfied by the morning of Day 12, subjects will continue to be confined in the CRU until these criteria are met, up to a maximum of Day 22. Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator (or designee).
[c] Subjects will receive a Follow-up Call approximately 7 days after CRU Discharge.

Figure 3 Study Design Schematic: Part 2

Screening	Check-in	Dosing[a]	LOXO-305, [^{14}C]-LOXO-305, and Total Radioactivity Concentrations	Clinic (CRU) Discharge	Follow-up Call[b]
Days -29 to -2	Day -1	Day 1	Day 1 to Day 9	Day 9	Approximately 7 days after Clinic (CRU) Discharge
	CRU Confinement				

CRU = Clinical Research Unit
[a] Following an overnight fast of at least 10 hours, a single oral dose of 200 mg of LOXO-305 administered as 2 × 100-mg tablets and a single intravenous (IV) dose of < 100 µg of [^{14}C]-LOXO-305 (containing ~1 µCi of radioactivity [microtracer]) administered by IV push 2 hours after the oral dose.
[b] Subjects will receive a Follow-up Call approximately 7 days after CRU Discharge.

Part 1:

After a Screening period of up to 28 days, subjects will check in to the Clinical Research Unit (CRU) on Day -1 to confirm eligibility and to become familiar with study procedures. On the morning of Day 1, following an overnight fast of at least 10 hours, subjects will receive a single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) administered as an oral solution. Subjects will be confined at the CRU from the time of Check-in (Day -1) until Clinic Discharge (between Days 12 and 22). After completing discharge procedures, subjects will be discharged from the CRU as early as Day 12 and up to Day 22, provided recovery of radioactivity has reached the following threshold values:

- Plasma radioactivity below the limit of quantification for 2 consecutive collections, and
- ≥ 90% of the radioactive dose is recovered, and

- ≤ 1% of the radioactive dose per day is recovered in excreta (urine and feces) for 3 consecutive days on which a fecal sample is collected.

Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator (or designee). Subjects will receive a Follow-up Call approximately 7 days after Clinic Discharge.

Samples for determination of LOXO-305 concentrations in plasma, total radioactivity concentrations in plasma, whole blood, urine, and feces, and for metabolite profiling/characterization will be obtained through at least 264 hours postdose (Day 12), and possibly up to 504 hours postdose (Day 22). A Schedule of Assessments for Part 1 is presented in Appendix 4.

For subjects experiencing emesis within 4 hours following dosing, vomitus will be collected. The Medical Monitor (or designee) should be contacted immediately for further instructions and to determine if the subject should continue the study. All vomitus collected will be stored for possible analysis, as deemed appropriate.

Part 2:

After a Screening period of up to 28 days, subjects will check in to the CRU on Day -1 to confirm eligibility and to become familiar with study procedures. On the morning of Day 1, following an overnight fast of at least 10 hours, subjects will receive a single oral dose of 200 mg of LOXO-305 as 2 × 100-mg tablets and 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. Subjects will be confined at the CRU from the time of Check-in (Day -1) until Day 9 and will be discharged from the CRU after completing all discharge procedures. Subjects will receive a Follow-up Call approximately 7 days after Clinic Discharge.

Samples for determination of LOXO-305 concentrations in plasma, and total radioactivity and [^{14}C]-LOXO-305 concentrations in plasma, urine, and feces will be obtained through 192 hours postdose (Day 9). A Schedule of Assessments for Part 2 is presented in Appendix 4.

Part 1 and Part 2

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

the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through End of Treatment [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.

3.2. Discussion of Study Design

Part 1 of this study is designed to evaluate the AME kinetics of LOXO-305 using radiolabeled drug in healthy adult male subjects to support its further development and registration. Part 1 will also allow for identification and characterization of any metabolites of LOXO-305 that are produced following oral dosing. Analysis of total radioactivity and metabolites in urine and feces will provide information about the extent of urine and fecal excretion of LOXO-305 and its metabolites.

Part 2 is designed to determine the absolute bioavailability of LOXO-305 by comparing its plasma exposure following oral dosing to the plasma exposure of [^{14}C]-LOXO-305 following IV microtracer administration. The IV microtracer method allows for simultaneous oral and IV dosing in the same subjects, which is expected to result in less variability in absolute bioavailability estimates. The IV dose of [^{14}C]-LOXO-305 will be administered so that peak plasma concentrations of [^{14}C]-LOXO-305 occur approximately at the t_{max} of LOXO-305 following oral dosing. Analysis of urine and fecal concentrations of [^{14}C]-LOXO-305 and total radioactivity will allow for determination of the amount and percentage of LOXO-305 excreted unchanged in urine and feces.

In Part 2, a microtracer (~1 μCi of radioactivity) of [^{14}C]-LOXO-305 will be used. This low level of radioactivity necessitates the use of accelerator mass spectrometry (AMS) as a more sensitive analytical method for detecting the low levels of radioactivity in plasma, urine, and fecal samples.

The study will be open-label because the study measures are objective outcomes (eg, PK parameters, total radioactivity in select biological matrices, metabolite profiling/characterization). Female subjects will be excluded to align with regulatory guidance. The "as low as (is) reasonably achievable" (ALARA) principle prescribed by the FDA[12] recommends that radiation exposure to subjects should be kept ALARA; therefore, if no specific reason exists to include females (ie, no available data suggest metabolism of LOXO-305 is different in females versus males), then the radiation exposure to female subjects should ideally be kept at zero by not including females in this radioactivity study and only enrolling and dosing male subjects. Conducting the study in healthy subjects will allow the evaluation of LOXO-305 metabolism and bioavailability in the absence of concomitant medications and comorbidities. The dose, subject population, study duration, and sample collection timing are considered adequate to achieve the study objectives.

3.3. Selection of Doses in the Study

Single oral doses of 200 mg LOXO-305 will be evaluated as this has been chosen as the recommended Phase 2 dose for the ongoing global Phase 1/2 first-in-human study, LOXO-BTK-18001 (BRUIN Study). Doses of LOXO-305 from 25 mg QD to 300 mg QD

have been evaluated in the ongoing global Phase 1/2 first-in-human study, LOXO-BTK-18001 (BRUIN Study) in patients with previously treated CLL/SLL or NHL with dose escalation up to 300 mg QD approved by the study's Safety Review Committee. The available data demonstrate that LOXO-305 appears safe and well tolerated at these doses. At all evaluated doses, including oral doses of up to 300 mg QD, no dose-limiting toxicities have been identified in humans.[1] A <100 µg dose has been chosen as the IV microdose to permit dosing without supporting IV toxicology data.[10]

For Part 1, the planned radioactive dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) is expected to provide a sufficient radioactive signal to achieve the study objectives with minimal radiation risk to subjects. Based on the dosimetry analysis in pigmented rats, the overall whole-body radiation dose in a male subject after administration of a single 100-µCi (3.7-MBq) oral dose of [^{14}C]-LOXO-305 was calculated to be 120 mrem (1.2 mSv) when using allometric conversion.[11] This value is well below the FDA exposure limit of 3000 mrem after a single dose for human isotope studies.[12] Based on the PK and available dosimetry data, administration of a single 200-µCi (7.4-MBq) oral dose of [^{14}C]-LOXO-305 would not be expected to represent a significant radiation exposure risk when administered to healthy male subjects in a clinical trial.

For Part 2, the radioactive dose of ~1 µCi of [^{14}C]-LOXO-305 (microtracer) is only about 0.5% of the radioactive dose planned for Part 1 and will present minimal radiation risk to healthy subjects. The low levels of radioactivity planned for Part 2 will necessitate the use of AMS as a highly sensitive analytical technique for quantifying the radioactivity in plasma, urine, and fecal samples. The radioactive dose of ~1 µCi together with the use of AMS for analysis of radioactivity is expected to allow for completion of study objectives of Part 2 with minimal radiation exposure risk to healthy subjects.

4. SELECTION OF STUDY POPULATION

4.1. Screening Procedures

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

1. Inclusion/Exclusion criteria
2. Informed consent
3. Demographic data
4. Medical history (including review of medication[s])
5. Height, weight, and body mass index (BMI)
6. 12-lead ECG measured after the subject has been resting in the supine position for at least 10 minutes (Section 7.2.4)
7. Vital sign measurements (including oxygen saturation, oral temperature, respiratory rate, and supine blood pressure [BP] and pulse rate [measured after the subject has been supine for at least 5 minutes]; Section 7.2.3)
8. HDYF? inquiry, AE, SAE, and concomitant medication evaluations (Section 7.2.1)

9. Clinical laboratory evaluations (Section 7.2.2; clinical chemistry panel [fasted at least 8 hours], coagulation parameters, hematology panel, and UA; Appendix 2)
10. Screens for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV) core antibody, human immunodeficiency virus (HIV) antibody, and SARS-CoV-2 (COVID-19) via polymerase chain reaction testing (PCR) or equivalent Appendix 2)
11. Hemoglobin A1c (HbA1c) test (Appendix 2)
12. Estimated glomerular filtration rate (Appendix 2)
13. Screen for selected drugs of abuse, including cotinine and alcohol (Appendix 2)
14. Thyroid-stimulating hormone (TSH) test (Appendix 2).

4.2. Check-in Procedures (Day -1)

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

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

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

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

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

4.3. Inclusion Criteria

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

1. Males, of any race, between 18 and 55 years of age, inclusive, at Screening.
2. Within BMI range of 18.5 and 32.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, or clinical laboratory evaluations (Appendix 4) at Screening and/or Check-in (Day -1) as assessed by the Investigator (or designee).
4. Subjects who are capable of fathering a child must agree to use 1 of the following methods of contraception from the time of the dose administration through 6 months after the last dose of LOXO-305 administration:
    a. Sterilization, with documented confirmation of surgical success. Subjects will be surgically sterile for at least 90 days prior to Check-in (Day -1). If documentation is not available, subjects must follow 1 of the contraception methods below:
        i. Male condom with spermicide, or
        ii. Subject must ensure that their female partner meets 1 of the following criteria:
            1. intrauterine device (IUD) (hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
            2. established use of oral, implanted, injected, transdermal, intravaginal, or hormonal method of contraception associated with inhibition of ovulation; or
            3. non-childbearing potential, defined as being permanently sterile (ie, due to hysterectomy, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion more than 6 months prior to male partner's study drug administration); or
            4. be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone serum levels consistent with postmenopausal status.

    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 subject is abstinent at the time of signing the ICF but becomes

sexually active through 6 months after study drug administration, he must agree to use contraception as described above.

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

5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.
6. History of a minimum of 1 bowel movement per day.

4.4. Exclusion Criteria

The following will exclude potential subjects from the study:

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

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

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

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

blood cell count and platelet counts will be permitted up to 2 times to confirm eligibility for study participation if the values fall within normal ranges.

9. Positive serologic test for HBsAg, HBV core antibody, HCV, or HIV antibody at Screening. Subjects who are positive for HCV by antibody will require confirmation by PCR before enrollment to detect presence of active virus. Subjects who are HCV PCR positive or for whom a PCR is unable to be obtained will not be eligible.
10. Positive PCR test (or equivalent) for COVID-19 at Screening, Check-in (Day -1) or predose on Day 1. Further details regarding COVID-19 testing (including procedures who test positive at any time throughout CRU confinement) are specified in a separate document.
11. Subjects with known ongoing alcohol and/or drug abuse within 2 years prior to Screening, or evidence of such abuse as indicated by the laboratory assays for drugs of abuse (including cotinine and alcohol) conducted during Screening and/or at Check-in (Day -1). Tests for drugs of abuse must be negative at both Screening and Check-in (Day -1).
12. Consumption of grapefruit/grapefruit juice or Seville oranges or its juice within 7 days prior to Check-in (Day -1) and through EOT or ET.
13. Consumption of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
14. Strenuous exercise within 5 days prior to Check-in (Day -1) and through EOT or ET.
15. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
16. Participation in any other investigational study drug trial involving administration of any investigational drug in the past 30 days or 5 half-lives (if known), whichever is longer, prior to the first dose administration (Day 1).
17. Use or intention to use any prescription or over-the-counter medications (including but not limited to any moderate or strong CYP3A4 and/or CYP3A5 inhibitors or inducers [including herbal products such as St. John's wort], strong P-glycoprotein [P-gp] inhibitors, proton pump inhibitors, antacids, H2 receptor antagonists, and drugs that prolong QT/QTc interval, herbal products, natural or herbal supplements) within 14 days prior to the first dose administration (Day 1) and through EOT or ET, unless deemed acceptable by the Investigator (or designee) and Sponsor.
18. History of a major surgical procedure within 30 days prior to Screening.
19. History or presence, upon clinical evaluation, of any illness that, in the opinion of the Investigator (or designee), would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results, or put the subject at undue risk.
20. History or clinical manifestation of gastritis, gastrointestinal tract, metabolic, or hepatic disorder or other clinical condition that might, in the opinion of the Investigator (or designee), and as confirmed by the Sponsor, affect the absorption, distribution, biotransformation, or excretion of LOXO-305.
21. Poor peripheral venous access.

22. Donation of blood from 56 days prior to Screening, plasma or platelets from 4 weeks prior to Screening.
23. Receipt of blood products within 2 months prior to Check-in (Day -1).
24. Use of tobacco, smoking cessation products, or products containing nicotine within 3 months prior to Screening and through EOT or ET.
25. Significant history or clinical manifestation of any allergic, dermatological, biliary, renal, hematological, pulmonary, cardiovascular (including any prior history of cardiomyopathy or cardiac failure), neurological, or psychiatric disorder (as determined by the Investigator [or designee]), or cancer within the past 5 years (except localized basal cell, squamous, or in situ cancer of the skin).

    Note: subjects with a history of uncomplicated appendectomy and/or hernia repairs will be acceptable.
26. History of congenital non-hemolytic hyperbilirubinemia (eg, Gilbert's syndrome).
27. History of diabetes mellitus; HbA1c $\geq$ 6.5%.
28. Has previously completed or withdrawn from any other study investigating LOXO-305 and have previously received the investigational product.
29. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator (or designee), and as confirmed by the Sponsor, within the 30 days prior to the first dosing and through EOT or ET.
30. Exposure to significant diagnostic or therapeutic radiation (eg, serial X-ray, computed tomography scan, barium meal) or current employment in a job requiring radiation exposure monitoring within 12 months prior to Check-in (Day -1).
31. **Part 1 only**: Participation in a radiolabeled drug study where exposures are known to the Investigator (or designee) within the previous 4 months prior to Check-in (Day -1) or participation in a radiolabeled drug study where exposures are not known to the Investigator (or designee) within the previous 6 months prior to Check-in (Day -1). The total 12-month exposure from this study and a maximum of 2 other previous radiolabeled studies within 4 to 12 months prior to this study will be within the Code of Federal Regulations (CFR) recommended levels considered safe, per United States (US) Title 21 CFR 361.1: less than 5000 mrem whole body annual exposure with consideration given to the half-lives of the previous radiolabeled study drugs received.
32. **Part 2 only**: Participation in any other radiolabeled investigational study drug trial within 12 months prior to Check-in (Day -1). Any previous radiolabeled study drug must have been received more than 12 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). If subjects are withdrawn by the Investigator (or designee) or voluntarily withdraw prematurely from the study, replacement subjects may be enrolled only if deemed necessary by the Sponsor. If necessary, as determined by the Sponsor, subjects who fail to complete the treatment or have

insufficient PK data may be replaced. Replacement subjects will be assigned a subject number by adding 200 to the last 3 digits of the subject number for the subject they are replacing (eg, Subject Number 001-301 replaces Subject Number 001-101).

4.6. Removal of Subjects from Study Participation

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

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

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

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

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

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

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Active pharmaceutical ingredient (API) nonradiolabeled powder and tablets containing 100 mg LOXO-305) will be supplied by the Sponsor and radiolabeled API (powder) will be supplied by the Sponsor (or designee), along with the lot numbers and Certificates of Analysis. A Covance CRU licensed pharmacist will manufacture and label the IMP from bulk supplies, such that each unit dose contains a total of 200 mg LOXO-305 containing ~ 200 µCi of [^{14}C] for the Part 1 oral solution (Table 2) and < 100 µg LOXO-305 containing

approximately 1 µCi [^{14}C] for the Part 2 IV solution (Table 3). The completed drug product will be released by a Good Manufacturing Practice (GMP) Quality Auditor under GMP conditions prior to administration to subjects.

Table 2 Supplied Study Drugs: Part 1

Study Drug	[^{14}C]-LOXO-305	LOXO-305
Form[a]	Powder	Powder
Strength	N/A	N/A
Specific Activity	~50 µCi/mg	N/A
Supplier	Loxo Oncology, Inc.	Loxo Oncology, Inc.
Manufacturer	Eurofins BioPharma Product Testing	Olon Ricerca Bioscience

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

Table 3 Supplied Study Drugs: Part 2

Study Drug	LOXO-305	[^{14}C]-LOXO-305
Form[a]	Oral Tablet	Powder
Strength	100 mg	N/A
Specific Activity	N/A	~50 µCi/mg
Supplier	Loxo Oncology, Inc.	Loxo Oncology, Inc.
Manufacturer	Bend Research, Inc.	Eurofins BioPharma Product Testing

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

The Sponsor will supply a sufficient quantity of the applicable IMP and API for the manufacture of the respective unit doses at Covance CRU. All excipients will be sourced by Covance. Specific instructions regarding dose preparation will be mutually agreed upon between the Sponsor and the appropriate clinical staff and will be presented in a separate document.

The API and IMP will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

5.2. Study Treatment Administration

In Part 1, subjects will receive a single oral dose of 200 mg of [^{14}C]-LOXO-305 (containing ~200 µCi) as an oral solution with 240 mL of room temperature water. In Part 2, subjects will receive a single oral dose of 200 mg LOXO-305 as 2 × 100-mg tablets with 240 mL of room temperature water followed 2 hours later by a single dose of < 100 µg [^{14}C]-LOXO-305 (containing ~1 µCi radioactivity [microtracer]) as an IV push over approximately 2 minutes. In both parts, an additional 100 mL of water may be administered if needed.

In Parts 1 and 2, oral dosing will be preceded by an overnight fast (ie, at least 10 hours) from food (not including water) and will be followed by a fast from food (not including water) for at least 4 hours post-oral dose. During Part 2, subjects may receive lunch approximately 2 hours after receiving the IV dose. Except as part of dose administration, subjects will restrict their consumption of water for 1 hour prior to oral dose and for 1 hour post-oral dose. At all other times during the study, subjects may consume water ad libitum.

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

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

Subjects will be instructed not to crush, split, or chew oral LOXO-305 tablets.

All oral doses will be administered while the subjects are seated and subjects will not be permitted to lie supine for 4 hours' post-oral dose except as necessitated by the occurrence of an AE(s) and/or study procedures. Subjects may be asked to be semi-supine/supine for the IV dosing.

Except when they are using the toilet, study subjects will be observed for approximately 4 hours post-oral dose to ensure that they are not experiencing AEs, becoming nauseated, or experiencing emesis.

5.3. Randomization

This is a nonrandomized study.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

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

5.6. Drug Accountability

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

For oral unit doses containing ^{14}C, the empty used unit dose containers will undergo radioanalysis to determine the amount of any residual radioactivity remaining after dose administration and be discarded upon satisfactory completion of the compliance and

accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies (including all IMP and API) will be disposed of by the CRU, per the Sponsor's written instructions and/or in accordance with local/state/federal guidelines governing waste disposal of investigational drugs and the CRUs Standard Operating Procedures.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

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

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

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

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

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

6.2. Diet, Fluid, and Activity Control

While confined at the CRU, subjects will receive a standardized high fiber diet at scheduled times that do not conflict with other study-related activities. Pitted prunes or prune juice may be given on an as-needed basis to aid in normal bowel function and will not be considered a concomitant medication.

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

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

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

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

Fasting requirements in relation to dosing are described in Section 3.1 and Section 5.2. Fasting requirements in relation to collection of blood for clinical laboratory evaluations are described in Section 7.2.2 and Appendix 4.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic, Total Radioactivity, and Metabolite Profiling Blood Sample Collection and Processing

Blood samples for PK analysis for determination of LOXO-305, total radioactivity, and metabolite profiling and identification in Part 1 and for LOXO-305, [^{14}C]-LOXO-305, and total radioactivity in Part 2 will be collected at the times indicated in the Schedule of Assessments (Appendix 4). Blood samples will be collected from the contralateral arm to the arm/hand used for IV dose administration. Procedures for collection, processing, and shipping of blood samples will be detailed in a separate document.

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

7.1.2. Pharmacokinetic, Total Radioactivity, and Metabolite Profiling Urine and Feces Collection and Processing

Urine will be collected over the time intervals indicated in the Schedule of Assessments in Appendix 4 for determination of total radioactivity and metabolite profiling and identification for Part 1 and for [^{14}C]-LOXO-305 concentration and total radioactivity in Part 2. Procedures for collection, processing, and shipping of urine collections will be detailed in a separate document.

Feces will be collected over the time intervals indicated in the Schedule of Assessments in Appendix 4 for determination of total radioactivity in Parts 1 and 2, metabolite profiling and identification for Part 1 (where possible), and for measurement of [^{14}C]-LOXO-305 in Part 2. If possible, a single baseline fecal sample will be collected from after Check-in on Day -1 until predose on Day 1. Procedures for collection, processing, and shipping of feces collections will be detailed in a separate document.

7.1.3. Vomitus Sample Collection

In Part 1, for subjects experiencing emesis within 4 hours following oral dosing, vomitus will be collected. Attempts will be made to collect vomitus from subjects experiencing emesis after 4 hours postdose. All vomitus collected will be stored for possible analysis as deemed appropriate.

7.1.4. Analytical Methodology

In Parts 1 and 2, plasma concentrations of LOXO-305 will be determined using a validated bioanalytical method.

In Part 1, total radioactivity in plasma, whole blood, urine, and feces will be determined with liquid scintillation counting (LSC). Profiling and identification of metabolites in plasma, urine, and, where possible, feces will be conducted using standard laboratory procedures.

In Part 2, concentrations of [^{14}C]-LOXO-305 in plasma, urine, and feces will be determined using high performance liquid chromatography fractionation followed by AMS. Concentrations of total radioactivity in plasma, urine and feces will be determined using AMS and/or LSC. Specifics of the analytical methods will be provided in separate documents.

7.2. Safety and Tolerability Assessments

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

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

- dosing
- PK, total radioactivity, and metabolite profiling and identification blood sampling
- start and end of urine and fecal collections (for drug assay)
- vital sign measurements
- 12-lead ECGs
- blood and urine samples for clinical laboratory evaluations
- physical examination.

7.2.1. Adverse Events

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

Subjects will be asked a non-leading HDYF? question such as “Have there been any changes in your health status since Screening/since you were last asked?” at the timepoints specified

in Appendix 4 (ie, at Screening [after the ICF is signed], at Check-in [Day -1], at each postdose vital sign measurements, and at an appropriate time for all other days). Subjects will also be encouraged to voluntarily report AEs occurring at any other time through the EOS.

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

Unless a subject withdraws consent or is withdrawn from the study and does not complete the Follow-up Phone Call, all subjects must be followed until EOS. Subjects with AEs that are assessed as related to study drug by the Investigator (or designee) 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 (RSI) in the current IB[1] for LOXO-305 for additional safety information.

7.2.2. Clinical Laboratory Evaluations

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

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

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

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

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

7.2.3. Vital Signs

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

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

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

7.2.4. 12-Lead Electrocardiogram

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

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

7.2.5. 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

No formal statistical assessment of sample size has been conducted as this study does not have a hypothesis. The sample size chosen for this study is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the study. Six subjects will participate in each part of the study. Each subject will participate in either Part 1 or Part 2. In the event of early withdrawal of any subjects and/or to ensure 6 subjects complete each part of the study, replacement subjects may be enrolled at the discretion of the Sponsor.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The **PK population** will include all subjects who received at least 1 dose of LOXO-305 or [^{14}C]-LOXO-305 and have evaluable PK data. At the discretion of the Sponsor, a subject may be excluded from the PK summary statistics and statistical analysis. The impact of protocol deviations on PK population will be evaluated on a case-by-case basis.

8.2.2. Safety Population

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

8.3. Pharmacokinetic Analyses

Part 1

Samples for determination of LOXO-305 concentrations in plasma, total radioactivity concentrations in plasma, whole blood, urine, and feces, and for metabolite profiling/characterization will be obtained through at least 264 hours postdose (Day 12), and possibly up to 504 hours postdose (Day 22). Pharmacokinetic parameters (where applicable) will be calculated using standard noncompartmental methods.

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

$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 extrapolated to infinity, calculated using the formula: $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + (C_{last} \div \lambda_z)$ where C_{last} is the last quantifiable concentration and λ_z is the apparent terminal elimination rate constant
$AUC_{0\text{-}t}$	area under the concentration-time curve from hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
C_{max}	maximum observed concentration

t_{max}	time to maximum observed concentration
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t½ = \ln(2)/ \lambda_z$
CL/F	apparent systemic clearance (LOXO-305 only)
V_z/F	apparent volume of distribution during the terminal phase (LOXO-305 only)
$AUC_{0\text{-}inf}$ Plasma LOXO-305/Total Radioactivity Ratio	$AUC_{0\text{-}inf}$ of plasma LOXO-305 relative to $AUC_{0\text{-}inf}$ of plasma total radioactivity
$AUC_{0\text{-}inf}$ Blood/ Plasma Ratio	$AUC_{0\text{-}inf}$ of whole blood total radioactivity to $AUC_{0\text{-}inf}$ of plasma total radioactivity

Whenever possible, the following PK parameters will be calculated for each subject based on the urine concentrations of total radioactivity:

A_{eu}	amount excreted in urine per sampling interval
cumulative A_{eu}	cumulative amount excreted in urine
f_{eu}	percentage of dose excreted in urine per sampling interval, where $\%f_{eu} = 100 (A_{eu}/\text{dose})$
cumulative f_{eu}	cumulative percentage excreted in urine

Whenever possible, the following PK parameters will be calculated for each subject based on the fecal concentrations of total radioactivity:

A_{ef}	amount excreted in feces per sampling interval
cumulative A_{ef}	cumulative amount excreted in feces
f_{ef}	percentage of dose excreted in feces per sampling interval, where $\%f_{ef} = 100 (A_{ef}/\text{dose})$
cumulative f_{ef}	cumulative percentage excreted in feces

Additionally, the metabolic profile of LOXO-305 and the identification of LOXO-305 metabolites will be determined for each subject. Pharmacokinetic parameters for relevant metabolites of LOXO-305 may be calculated for each subject in Part 1, as deemed appropriate, based on plasma, urine, and/or fecal concentration levels.

Part 2

Samples for determination of LOXO-305 concentrations in plasma, and total radioactivity and [^{14}C]-LOXO-305 concentrations in plasma, urine, and feces will be obtained through 192 hours postdose (Day 9).

Pharmacokinetic parameters (where applicable) will be calculated using standard noncompartmental methods.

Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of [^{14}C]-LOXO-305, LOXO-305, and total radioactivity:

$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 extrapolated to infinity, calculated using the formula described above
$AUC_{0\text{-}t}$	area under the concentration-time curve from hour 0 to the last measurable concentration, calculated as described above
C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t½ = \ln(2)/ \lambda_z$
CL/F	apparent systemic clearance (LOXO-305 only)
V_z/F	apparent volume of distribution during the terminal phase (LOXO-305 only)
F	absolute bioavailability, calculated using the formula: $F = \frac{AUC_{0\text{-}inf}\text{(oral) x Dose (IV)}}{AUC_{0\text{-}inf}\text{(IV) x Dose (oral)}}$
CL	total clearance ([^{14}C]-LOXO-305 only)
V_z	volume of distribution ([^{14}C]-LOXO-305 only)
V_{ss}	volume of distribution at steady state ([^{14}C]-LOXO-305 only)

In addition, whenever possible, the following PK parameters will be calculated for each subject based on the urine concentrations of [^{14}C]-LOXO-305 and total radioactivity:

A_{eu}	amount excreted in urine
cumulative A_{eu}	cumulative amount excreted in urine
f_{eu}	percentage of dose excreted in urine, calculated as described above

cumulative f_{eu}	cumulative percentage excreted in urine
CL_R	renal clearance ([^{14}C]-LOXO-305 only)

Whenever possible, the following PK parameters will be calculated for each subject, based on the fecal concentrations of [^{14}C]-LOXO-305 and total radioactivity:

A_{ef}	amount excreted in feces
cumulative A_{ef}	cumulative amount excreted in feces
f_{ef}	percentage of dose excreted in feces, calculated as described above
cumulative f_{ef}	cumulative percentage excreted in feces

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

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

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

8.3.1. Descriptive Analysis

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

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

8.3.2. Statistical Methodology

No formal statistical analyses are planned.

8.4. Safety Analysis

All safety assessments, including AEs and SAEs, vital sign measurements, clinical laboratory results, physical examination results, concomitant medications, and 12-lead ECGs, will be tabulated and summarized, where possible, using descriptive methodology, as needed, by timepoint. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of LOXO-305 in each part. 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 or higher). Adverse events will be coded

using MedDRA Version 22.1 (or higher). The incidence of AEs will be presented by severity and by relationship to study drug as determined by the Investigator or designee (Appendix 1 for AE reporting). All TEAEs will be summarized by SOC and PT.

8.5. Data Handling and Record Keeping

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

The Data Management Plan will be approved by the Sponsor.

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

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

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

8.6. Quality Control and Quality Assurance

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

9. ADMINSTRATIVE ASPECTS

9.1. Change in Protocol

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

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

9.2. Site Initiation Visit/Investigator Meeting

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

9.3. Disclosure

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

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

9.4. Monitoring

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

9.5. Institutional Review Board

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

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

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

9.6. Informed Consent

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

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

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

9.7. Records

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

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

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

9.8. Reference to Declaration of Helsinki/Basic Principles

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

9.9. Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

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11. APPENDICES

Appendix 1: Adverse Event Reporting

Adverse Events

Definition of Adverse Events

An 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 TEAE is an AE that starts on or after the first administration of study drug.

The following are all AEs:

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

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

Categorization of Adverse Events

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

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

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

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

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

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

Pregnancy

As information is available, a pregnancy in female partners of male subjects diagnosed through EOS or ET (if the subject discontinues from the study and does not complete a Follow-up Phone Call) and for up to 90 days after study drug administration should be reported by the Investigator (or designee) via email to Covance or the Sponsor's Clinical Safety Representative within 24 hours of first awareness. 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

If possible, the subject's 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.

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

All pregnancies should be recorded on the required pregnancy forms.

Definition of Serious Adverse Events

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

- Death;

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

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

Unexpected Adverse Drug Reaction

An AE or suspected adverse drug reaction is considered 'unexpected' if the event is not listed in the Reference Safety Information section of the IB or if it is not listed at the specificity or severity that has been observed for an unapproved IMP.

Reporting

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

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

email: SAEIntake@covance.com

To report the SAE, the completed report form should be sent by email to Covance or the Sponsor's Clinical Safety Representative within 24 hours of awareness. Incoming reports are reviewed during normal business hours. Additional reporting instructions and the SAE Report Form are provided in the Study Manual.

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

Appendix 2: Clinical Laboratory Evaluations

<table>
<tr><th>Clinical Chemistry Panel (Fasted):</th><th>Hematology Panel:</th><th></th></tr>
<tr><td rowspan="4">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</td><td rowspan="4">Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential (percent and absolute):
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils</td><td>Coagulation Parameters:</td></tr>
<tr><td>Partial thromboplastin time
Prothrombin time
International normalized ratio</td></tr>
<tr><td>Serology:[b]</td></tr>
<tr><td>Human immunodeficiency virus (HIV) antibody
Hepatitis B surface antigen (HBsAg)
Hepatitis B virus (HBV) core antibody
Hepatitis C virus (HCV) antibody</td></tr>
<tr><td>Urine Drug Screen:[a]</td><td>Urinalysis:</td><td>Other Tests:</td></tr>
<tr><td>Including but not limited to the following:
Alcohol (ethanol)
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine</td><td>Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic examination including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)</td><td>Hemoglobin A1c (HbA1c)[b]
Estimated glomerular filtration rate[a,c]
Thyroid-stimulating hormone (TSH)[b]
SARS-CoV-2 (COVID-19) test</td></tr>
</table>

a. Performed at Screening and Check-in (Day -1) only.
b. Performed at Screening only.
c. Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

Appendix 3: Total Blood Volume

The following blood volumes are the maximum that will be withdrawn for each subject.

Part 1:

	Volume per blood sample (mL)	Up to Day 22[a]	
		Maximum number of blood samples	Total amount of blood (mL)
Clinical Laboratory evaluations Chemistry[b] Hematology Coagulation	CCI		
Hemoglobin A1c (HbA1c)			
Serology			
Plasma for LOXO-305 concentration			
Whole blood and plasma for total radioactivity			
Plasma for metabolite profiling and identification			
Total:			

[a] Subjects could be discharged on Day 12 if the discharge criteria are met or may be resident within the Clinical Research Unit for additional 24-hour sample collections of LOXO-305 concentration in plasma, total radioactivity in blood and plasma, LOXO-305 metabolite in plasma, and total radioactivity in urine and feces up to Day 22. Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator (or designee).
[b] Thyroid stimulating hormone and estimated glomerular filtration rate will be assessed as part of the clinical chemistry sample.

Part 2:

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical Laboratory evaluations Chemistry[a] Hematology Coagulation	CCI		
Hemoglobin A1c (HbA1c)			
Serology			
Plasma for LOXO-305 concentration			
Plasma for [^{14}C]-LOXO-305 concentration and total radioactivity			
Total:			

[a] Thyroid stimulating hormone and estimated glomerular filtration rate will be assessed as part of the clinical chemistry sample.

If additional blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 600 mL for Part 1 and 350 mL for Part 2.

Appendix 4: Schedule of Assessments

	Schedule of Assessments: Part 1														
			Study Day											**Clinic Discharge/ EOT[k] or ET[u]**	**Follow-up Phone Call (EOS)**
Study Procedures[a]	**Screening (Days -29 to -2)**	**Check-in (Day -1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Day 12 to Day 22[k,u]**	**7 (±2) days post EOT or ET[v]**
Confined to the CRU		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]													
Estimated Glomerular Filtration Rate	X	X													
Physical Examination[d]		X												X	
12-lead ECG[e]	X	X	X			X					X			X	
Vital Signs[f]	X[g,h]	X[g,h]	X[h]	X	X	X	X	X	X	X	X	X	X	X[g, h]	
HDYF? Inquiry[i]	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
LOXO-305 Dosing ([^{14}C]-LOXO-305)			X												
Blood Sampling for LOXO-305 Concentration (Plasma)[l]			X	X	X	X	X	X	X	X	X	X	X	X	
Blood Sampling for Total Radioactivity (Whole Blood and Plasma)[l]			X	X	X	X	X	X	X	X	X	X	X	X	
Blood Sampling for Metabolite Profiling			X	X	X	X	X	X	X	X	X	X	X	X	

	Schedule of Assessments: Part 1														
			Study Day											Clinic Discharge/ EOT[k] or ET[u]	Follow-up Phone Call (EOS)
Study Procedures[a]	**Screening (Days -29 to -2)**	**Check-in (Day -1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Day 12 to Day 22[k,u]**	**7 (±2) days post EOT or ET[v]**
and Identification (Plasma)[m]															
Urine Collection for Total Radioactivity and Metabolite Profiling and Identification[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Feces Collection for Total Radioactivity and Metabolite Profiling and Identification[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Laboratory Evaluations[p]	X	X				X			X		X			X[q]	
Hepatitis and HIV Screen	X														
COVID-19 Test[r]	X	X	X												
HbA1c Test	X														
Drug Screen[s]	X	X													
Prior and Concomitant Medications[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH Test	X														

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

a. For details on study procedures, see Section 7.
b. Interim medical history only.
c. Height collected at Screening only, BMI based on Screening height.
d. A complete physical examination will be performed at Check-in (Day -1). An abbreviated physical examination will be performed on the day of Clinic Discharge (EOT) or ET.

e. 12-lead ECGs will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws at Screening and Check-in (Day -1), Day 1 (predose and 2 hours after LOXO-305 dosing), Days 4, 9, 14 (if a subject is in the CRU), 19 (if the subject is in the CRU) and on the day of Clinic Discharge (EOT) or ET.
f. Vital sign measurements (supine BP and pulse rate) will be obtained at Screening and Check-in (Day -1), Day 1 (predose and 2 hours after LOXO-305 dosing), and daily (24-hour intervals) up to and including day of Clinic Discharge (EOT) or ET. When scheduled at the same nominal times, postdose vital sign measurements are to be performed prior to postdose PK blood draws (see Section 7.2). Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.
g. Oral temperature and respiratory rate will also be obtained at Screening, Check-in (Day -1), and on the day of Clinic Discharge (EOT) or ET.
h. Oxygen saturation will be measured at Screening, Check-in (Day -1), predose on Day 1, and on the day of Clinic Discharge (EOT) or ET.
i. An HDYF? inquiry will be performed at Screening (after the ICF is signed), at Check-in (Day -1), at each postdose vital sign measurements, and at an appropriate time for all other days.
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. Subjects can be discharged on Day 12 if the following discharge criteria are met: Plasma radioactivity below the limit of quantification for 2 consecutive collections, and ≥ 90% of the radioactive dose is recovered, and ≤ 1% of the radioactive dose per day is recovered in excreta (urine and feces) for 3 consecutive days on which a fecal sample is collected. If all discharge criteria are not met, subjects will be asked to remain resident within the Clinical Research Unit (CRU) and will continue until these criteria are met, up to a maximum of Day 22. If a subject does not meet the discharge criteria on Day 12, additional blood samples will be collected for LOXO-305 plasma, total radioactivity plasma and whole blood concentrations, LOXO-305 metabolite in plasma, and total radioactivity in urine and feces at 24-hour intervals until the day of Clinic Discharge (EOT or ET). Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator (or designee).
l. Blood samples for determination of LOXO-305 concentration (plasma) and total radioactivity (plasma and whole blood) will be collected prior to dosing (within 30 minutes) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, and 264 hours postdose (Day 12). If a subject does not meet the discharge criteria on Day 12, additional blood samples will be collected for LOXO-305 plasma and total radioactivity plasma and whole blood concentrations at 24-hour intervals until the day of Clinic Discharge (EOT) or ET. Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator (or designee). The allowed sampling window for blood samples for determination of LOXO-305 concentration (plasma) and total radioactivity (plasma and whole blood) will be the following: within 15 minutes prior to dosing for any of the predose sample timepoints; ± 5 minutes for sampling timepoints within the first 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours; and ± 60 minutes for the sampling timepoints ranging from 48 to 504 hours.
m. Blood samples for metabolite profiling/characterization will be collected at 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, and 264 hours postdose (Day 12). If a subject does not meet the discharge criteria on Day 12, additional blood samples will be collected for metabolite profiling/characterization at 24-hour intervals until the day of Clinic Discharge (EOT) or ET. The allowed sampling window for blood samples for metabolite profiling/characterization will be the following: within 15 minutes prior to dosing for any of the predose sample timepoints; ± 5 minutes for sampling timepoints within the first 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours; and ± 60 minutes for the sampling timepoints ranging from 48 to 504 hours. Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator (or designee).
n. Urine samples for determination of total radioactivity and metabolite profiling/characterization will be collected from 12 hours prior to dose administration (-12 to 0 hours predose); from 0 to 6, 6 to 12, and 12 to 24 hours; and for 24-hour intervals up to and including 264 hours postdose (Day 12). If a subject does not meet the discharge criteria on Day 12, additional urine samples will be collected at 24-hour intervals until the Day of Clinic Discharge (EOT) or ET.
o. If possible, a single baseline fecal sample will be collected from after Check-in on Day -1 until just prior to dose administration on Day 1. Postdose fecal samples for determination of total radioactivity and metabolite profiling/characterization will be collected from 0 to 24 hours postdose and for 24-hour intervals from Day 2 up to and including 264 hours postdose (Day 12). If a subject does not meet the discharge criteria on Day 12, additional fecal samples will be collected at 24-hour intervals until discharge from the CRU (EOT) or ET.

p. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and UA will be performed. On the day prior to EOT (if the subject completes the study) or ET, subjects are not required to be fasted prior to clinical laboratory evaluations.
q. Clinical laboratory evaluations will be performed on Day 14 (if a subject is in the CRU), Day 19 (if the subject is in the CRU), and on the day prior to Clinic Discharge (EOT) or on the day of ET. Clinical laboratory evaluations will be performed on the day prior to subject release from the CRU if the subject completes the study (EOT). Clinical laboratory evaluations will be performed on the day of subject release from the CRU if the subject terminates early (ET).
r. Testing for COVID-19 will be conducted at a minimum at Screening, Check-in (Day -1), and predose on 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.
s. Drugs of abuse urine test, including cotinine and alcohol. Results from the drugs of abuse tests will be used to determine subject eligibility per the inclusion/exclusion criteria.
t. Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 14 days prior to study drug administration for prescription medications and non-prescription medications will be recorded on the subject's electronic Case Report Form.
u. EOT is defined as when the subject is released from the CRU following completion of all assessments through a minimum of Day 12 up to Day 22. ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital sign measurements, ECG, and abbreviated physical examination results are to be available for review by the Investigator (or designee) prior to subject release from the CRU at the EOT. Clinical laboratory results for clinical chemistry, hematology, coagulation, and UA 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 performed 7 days (± 2 days) following EOT or ET. EOS is defined as when the CRU contacts the subject by a follow-up phone call 7 days (± 2 days) after the EOT visit or ET visit to determine if any SAE or study drug-related AE has occurred since the EOT or ET visit. All subjects who received LOXO-305 (including subjects who are terminated early) will be contacted.

Schedule of Assessments: Part 2

Study Procedures[a]	Screening (Days -29 to -2)	Check-in (Day -1)	Study Day 1	2	3	4	5	6	7	8	Clinic Discharge/ EOT or ET[s] 9	Follow-up Phone Call (EOS) 7 (±2) days post EOT or ET[u]
Confined to the CRU		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]										
Estimated Glomerular Filtration Rate	X	X										
Physical Examination[d]		X									X	
12-lead ECG[e]	X	X	X			X					X	
Vital Signs[f]	X[g,h]	X[g,h]	X[h]	X	X	X	X	X	X	X	X[g,h]	
HDYF? Inquiry[i]	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
LOXO-305 and [^{14}C]-LOXO-305 Dosing[k]			X									
Blood Collection for LOXO-305 and [^{14}C]-LOXO-305 Concentration (Plasma) and Total Radioactivity (Plasma)[l]			X	X	X	X	X	X	X	X	X	
Urine Collection for [^{14}C]-LOXO-305 Concentration and Total Radioactivity [m]		X	X	X	X	X	X	X	X	X	X	
Fecal Collection for Total Radioactivity and		X	X	X	X	X	X	X	X	X	X	

Schedule of Assessments: Part 2												
			Study Day								Clinic Discharge/ EOT or ET[s]	Follow-up Phone Call (EOS)
Study Procedures[a]	**Screening (Days -29 to -2)**	**Check-in (Day -1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**7 (±2) days post EOT or ET[u]**
[^{14}C]-LOXO-305 Concentration[n]												
Clinical Laboratory Evaluations[o]	X	X				X			X	X[t]	X[t]	
Hepatitis and HIV Screen	X											
COVID-19 Test[p]	X	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
TSH Test	X											

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

a. For details on study procedures, see Section 7.
b. Interim medical history only.
c. Height collected at Screening only, BMI based on Screening height.
d. A complete physical examination will be performed at Check-in (Day -1). An abbreviated physical examination will be performed at Day 9 (EOT) or ET.
e. 12-lead ECGs will be collected after the subject has rested in the supine position for at least 10 minutes, and will be obtained prior to and as close as possible to the scheduled blood draws at Screening and Check-in (Day -1), Day 1 (pre-oral and IV LOXO-305 dosing and 2 hours after oral and IV LOXO-305 dosing), Day 4, and Day 9 (EOT) or ET.
f. Vital sign measurements (supine BP and pulse rate) will be obtained at Screening and Check-in (Day -1), Day 1 (pre-oral and IV LOXO-305 dosing and 2 hours after oral and IV LOXO-305 dosing), and daily (24-hour intervals) up to and including Day 9 (EOT) or ET. When scheduled at the same nominal times, postdose vital sign measurements are to be performed prior to postdose PK blood draws (see Section 7.2). Vital sign measurements should be carried out prior to and as close as possible to having blood drawn. Blood pressure and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.
g. Oral temperature and respiratory rate will be obtained at Screening, Check-in (Day -1), and on Day 9 (EOT) or ET.
h. Oxygen saturation will be measured at Screening, Check-in (Day -1), predose on Day 1, and on Day 9 (EOT) or ET.
i. An 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. A single oral dose of 200 mg of 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.
l. Blood samples for determination of LOXO-305 concentration (plasma) will be collected at the following timepoints relative to oral dosing: Prior to oral LOXO-305 dosing (within 30 minutes) and 0.5, 1, and 2 hours (just prior to IV dosing) after oral LOXO-305 dosing. Blood samples for determination of [^{14}C]-LOXO-305 concentration (plasma) and total radioactivity (plasma) will be collected at the following timepoints relative to oral dosing: 2 hours (just prior to IV dosing) after oral LOXO-305 dosing. Blood samples for determination of LOXO-305 and [^{14}C]-LOXO-305 concentration (plasma) and total radioactivity (plasma) will continue to be collected at the following timepoints relative to the start of IV [^{14}C]-LOXO-305 dosing: 2 minutes (at end of IV), 10 minutes, 20 minutes, 30 minutes, 45 minutes, and 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, and 192 hours postdose (Day 9 [EOT]), relative to the start of IV [^{14}C]-LOXO-305 dosing (ie, start of LOXO-305 IV push). The allowed sampling window for blood samples for determination of LOXO-305 concentration (plasma) and/or [^{14}C]-LOXO-305 concentration (plasma) and total radioactivity will be the following: within 15 minutes prior to dosing (oral or IV) for the predose sample timepoint; ± 1 minute for sampling timepoints within the first 30 minutes; ± 5 minutes for sampling timepoints > 30 minutes < 12 hours; ± 30 minutes for sampling timepoints > 12 hours < 36 hours and ± 60 minutes for the sampling timepoints ranging from 48 to 192 hours.
m. Urine samples for determination of [^{14}C]-LOXO-305 and total radioactivity will be collected from 12 hours prior to oral dose administration (12 to 0 hours predose); from 0 (time of oral dose) to 4 hours postdose relative to the start of IV dose administration; from 4 to 8, 8 to 12, and 12 to 24 hours postdose relative to the start of IV dose administration; and for 24 hour intervals up to and including 192 hours postdose (Day 9 [EOT]), relative to the start of IV dose administration.
n. If possible, a single baseline fecal sample will be collected from after Check-in on Day -1 until just prior to oral dose administration on Day 1. Postdose fecal samples for determination of [^{14}C]-LOXO-305 and total radioactivity will be collected from 0 (time of oral dose) to 12 hours postdose relative to the start of IV dose administration; from 12 to 24 hours postdose relative to the start of IV dose administration; and for 24-hour intervals up to and including 192 hours postdose (Day 9 [EOT]), relative to the start of IV dose administration.
o. Clinical chemistry panel (fasted for at least 8 hours), coagulation parameters, hematology panel, and UA will be performed. On Day 8 (if the subject completes the study) or at ET, 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, Check-in (Day -1), and predose on Day 1. Testing for COVID-19 may also be conducted periodically during the subject's CRU confinement, at the discretion of the Investigator (or designee). Tests will be performed by rapid polymerase chain reaction or equivalent.
q. Drugs of abuse urine test, including cotinine and alcohol. Results from the drug of abuse tests will be used to determine subject eligibility per the inclusion/exclusion criteria.
r. Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 14 days prior to study drug administration for prescription medications and non-prescription medications, will be recorded on the subject's electronic Case Report Form.
s. EOT is defined as when the subject is released from the CRU following completion of all assessments through Day 9 (EOT). ET is defined as when the subject is released from the CRU if the subject terminates the study early. Vital sign measurements, ECG, and abbreviated physical examination results are to be available for review by the Investigator (or designee) prior to subject release from the CRU on Day 9 (EOT) or ET. Clinical laboratory results for clinical chemistry, hematology, coagulation, and UA 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.
t. Clinical laboratory evaluations will be performed on the day prior to subject release from the CRU (Day 8) if the subject completes the study (EOT). Clinical laboratory evaluations will be performed on the day of subject release from the CRU if the subject terminates early (ET).
u. To be performed 7 days (± 2 days) following EOT or ET. EOS is defined as when the CRU contacts the subject by a follow-up phone call 7 days (± 2 days) after the EOT visit or ET visit to determine if any SAE or study drug-related AE has occurred since the EOT or ET visit. All subjects who received LOXO-305 (including subjects who are terminated early) will be contacted.