Protocol Amendment 2 J2G-OX-JZJT (LOXO-RET-18016)

A Phase 1, Open-label, Two-part Study to Investigate the Absorption, Metabolism and Excretion and the Absolute Bioavailbility of [14C]-LOXO-292 in Healthy Male Subjects

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A PHASE 1, OPEN-LABEL, TWO-PART STUDY TO INVESTIGATE THE ABSORPTION, METABOLISM, AND EXCRETION, AND THE ABSOLUTE BIOAVAILABILITY OF [^{14}C]-LOXO-292 IN HEALTHY MALE SUBJECTS

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for

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ABBREVIATIONS

ADL	Activities of Daily Living
A_{ef}	amount excreted in feces per sampling interval
A_{eu}	amount excreted in urine per sampling interval
AE	adverse event
ALARA	as low as (is) reasonably achievable
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AME	absorption, metabolism, and excretion
AMS	accelerator mass spectrometry
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AV	atrioventricular
BID	twice daily
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CL	systemic clearance
C_{last}	last quantifiable concentration
CL/F	apparent systemic clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
Cum A_{ef}	cumulative amount excreted in feces
Cum A_{eu}	cumulative amount excreted in urine
Cum $\%f_{ef}$	cumulative percentage of dose excreted in feces
Cum $\%f_{eu}$	cumulative percentage of dose excreted in urine
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic Case Report Form
ET	Early Termination
F	absolute bioavailability

FDA	Food and Drug Administration
$\%f_{ef}$	percentage of dose excreted in feces per sampling interval
$\%f_{eu}$	percentage of dose excreted in urine per sampling interval
GI	gastrointestinal
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous(ly)
λ_z	apparent terminal elimination rate constant
LFT	liver function test
LSC	liquid scintillation counting
PK	pharmacokinetic(s)
RBC	red blood cell
RET	rearranged during transfection
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SAP	Statistical Analysis Plan
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time to maximum observed concentration
TSH	thyroid-stimulating hormone
US	United States
V_{ss}	volume of distribution at steady state
V_z	volume of distribution during the terminal phase
V_z/F	apparent volume of distribution during the terminal phase
WBC	white blood cell

1 SYNOPSIS

Title of Study:	A Phase 1, Open-label, Two-part Study to Investigate the Absorption, Metabolism, and Excretion, and the Absolute Bioavailability of [^{14}C]-LOXO-292 in Healthy Male Subjects
Objectives:	Part 1: Primary: • To determine mass balance and routes of elimination of [^{14}C]-LOXO-292 following oral administration of a single 160-mg (~40 µCi) radiolabeled dose of LOXO-292 in healthy male subjects • To assess the pharmacokinetics (PK) of a single oral dose of LOXO-292 using [^{14}C]-LOXO-292 • To determine the whole blood and plasma concentrations of total radioactivity • To determine the urinary and fecal recovery of total radioactivity • To characterize and identify metabolites of [^{14}C]-LOXO-292 in plasma, urine, and feces. Secondary: • To assess the safety and tolerability of [^{14}C]-LOXO-292 (containing ~40 µCi). Part 2: Primary: • To determine the absolute bioavailability of LOXO-292 following a single oral dose of 160 mg of LOXO-292 along with an intravenous (IV) dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi) • To evaluate the PK of LOXO-292 following oral and IV dosing • To evaluate the urinary excretion of LOXO-292 following oral dosing and of [^{14}C]-LOXO-292 following IV dosing • To evaluate the fecal recovery of total radioactivity following IV dosing of [^{14}C]-LOXO-292. Secondary: • To assess the safety and tolerability of LOXO-292.
Methodology/Study Design:	This study will be an open-label, 2-part absorption, metabolism, excretion (AME) and absolute bioavailability study of [^{14}C]-LOXO-292. 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 kinetics of LOXO-292, to identify and characterize metabolites of LOXO-292, and to assess the safety and tolerability of [^{14}C]-LOXO-292. Subjects in Part 1 will be administered a single oral dose of 160 mg of [^{14}C]-LOXO-292 (containing ~40 µCi) as an oral solution. In order to complete 6 subjects, 6 will be enrolled (different subjects from those participating in Part 2), along with 2 alternates (to be dosed in the event that dosing is unsuccessful for any of the initial 6 subjects). In the event of early withdrawal of any subjects after the alternate subjects are released, replacement subjects may be enrolled at the discretion of the Sponsor. Part 2 is designed to determine the absolute bioavailability of LOXO-292, to evaluate the urinary excretion of LOXO-292 and [^{14}C]-LOXO-292, to evaluate the fecal excretion of [^{14}C]-LOXO-292, and to assess the safety and tolerability of LOXO-292. Subjects in Part 2 will be administered a single oral dose of 160 mg of LOXO-292 as 2 x 80-mg capsules followed 2 hours later by a single dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi) administered as an IV push over approximately 2 minutes. In order to complete 6 subjects, 6 will be enrolled (different subjects from those participating in Part 1), along with 2 alternates (to be dosed in the event that dosing is unsuccessful for

	any of the initial 6 subjects). In the event of early withdrawal of any subjects after the alternate subjects are released, 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. A subject who completes sufficient LOXO-292, [^{14}C]-LOXO-292 (Part 2 only), total radioactivity, and metabolite (Part 1 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 Safety Follow-up Call. The planned duration of study conduct for Part 1 is up to 59 days from Screening through the Safety Follow-up Call. The planned duration of study conduct for Part 2 is up to 46 days from Screening through the Safety Follow-up Call. <u>Part 1:</u> 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 8 hours, subjects will receive a single oral dose of 160 mg of [^{14}C]-LOXO-292 (containing ~40 µCi) administered as an oral solution. Subjects will be confined at the CRU from the time of Check-in until Clinic Discharge (between Days 8 and 22). After completing discharge procedures, subjects will be discharged from the CRU as early as Day 8 and up to Day 22, provided recovery of radioactivity has reached the following threshold values: • ≥ 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 confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the Sponsor and Investigator. Subjects will receive a Safety Follow-up Call approximately 7 days after Clinic Discharge. In this study, safety will be monitored with adverse event (AE) inquiries, clinical laboratory evaluations, vital signs measurements, 12-lead electrocardiograms (ECGs), and physical examinations during the study. Samples for determination of LOXO-292 concentrations in plasma, total radioactivity concentrations in plasma, whole blood, urine, and feces, and for metabolite profiling/characterization will be obtained through at least 168 hours postdose (Day 8), and possibly up to 504 hours postdose (Day 22). <u>Part 2:</u> 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 8 hours, subjects will receive a single oral dose of 160 mg of LOXO-292 as 2 x 80-mg capsules followed 2 hours later by a single dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi) administered as an IV push over approximately 2 minutes. Subjects will be confined at the CRU from the time of Check-in until Day 9 and will be discharged from the CRU after completing all discharge procedures. Subjects will receive a Safety Follow-up Call approximately 7 days after Clinic Discharge. As in Part 1, safety will be monitored with AE inquiries, clinical laboratory evaluations, vital signs measurements, 12-lead ECGs, and physical examinations during the study. Samples for determination of plasma and urine concentrations of LOXO-292 and [^{14}C]-LOXO-292 and for determination of total radioactivity concentrations in urine and feces will be obtained through 192 hours postdose (Day 9).

Number of Subjects:	Part 1: In order to complete 6 subjects, 6 will be enrolled (different subjects from those participating in Part 2), along with 2 alternates (to be dosed in the event that dosing is unsuccessful for any of the initial 6 subjects). Part 2: In order to complete 6 subjects, 6 will be enrolled (different subjects from those participating in Part 1), along with 2 alternates (to be dosed in the event that dosing is unsuccessful for any of the initial 6 subjects). In Parts 1 and 2, in the event of early withdrawal of any subjects after the alternate subjects are released, 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.
Test Product(s), Dose, and Mode of Administration:	Part 1: Subjects will receive a single oral dose of 160 mg of [^{14}C]-LOXO-292 (containing ~40 µCi) as an oral solution after at least an 8-hour fast. Part 2: Subjects will receive a single oral dose of 160 mg of LOXO-292 as 2 x 80-mg capsules after at least an 8-hour fast followed 2 hours later by a single dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi) administered as an IV push over approximately 2 minutes.
Duration of Treatment:	Planned Enrollment/Screening Duration: Part 1; approximately 28 days (Days -29 to -2). Part 2; approximately 28 days (Days -29 to -2). Length of 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 59 days (Screening to Safety Follow-up Call). Part 2; up to 46 days (Screening to Safety Follow-up Call).
Criteria for Evaluation: Safety	Safety will be monitored with AE inquiries, clinical laboratory evaluations, vital signs measurements, ECGs, and physical examinations.
Criteria for Evaluation: Pharmacokinetics	<u>Part 1:</u> Whenever possible, the following PK parameters will be calculated based on the plasma concentrations of LOXO-292 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 time 0 to the time of the last quantifiable concentration (AUC_{last}), AUC extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL/F; for LOXO-292 only), apparent volume of distribution during the terminal phase (V_z/F; for LOXO-292 only), $AUC_{0-\infty}$ of total radioactivity in whole blood/$AUC_{0-\infty}$ of total radioactivity in plasma (Blood/Plasma AUC Ratio), and $AUC_{0-\infty}$ of LOXO-292 in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma (Plasma LOXO-292/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 (Cum A_{eu}), percentage of dose excreted in urine per sampling interval (%f_{eu}), and cumulative percentage of dose excreted in urine (Cum %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 (Cum A_{ef}), percentage of dose excreted in feces per sampling interval (%f_{ef}), and cumulative percentage of dose excreted in feces (Cum %f_{ef}). <u>Part 2:</u> Following oral dosing of LOXO-292, the following PK parameters will be calculated, whenever possible, based on the plasma concentrations of LOXO-292: C_{max}, T_{max}, AUC_{last}, $AUC_{0-\infty}$, λ_z, $t_{1/2}$, absolute bioavailability (F), CL/F, and V_z/F. Following IV dosing of [^{14}C]-LOXO-292 (containing ~1 µCi), the following PK parameters will be calculated, whenever possible, based on the plasma concentrations of

	[^{14}C]-LOXO-292: C_{max}, T_{max}, AUC_{last}, $AUC_{0-\infty}$, λ_z, $t_{1/2}$, systemic clearance (CL), volume of distribution during the terminal phase (V_z), and volume of distribution at steady state (V_{ss}). The following PK parameters will be calculated, whenever possible, for each subject based on the urine concentrations of LOXO-292, [^{14}C]-LOXO-292, and total radioactivity: A_{eu}, Cum A_{eu}, renal clearance (CL_R; LOXO-292 and [^{14}C]-LOXO-292 only), $\%f_{eu}$, and Cum $\%f_{eu}$. The following PK parameters will be calculated, whenever possible, for each subject based on the fecal concentrations of total radioactivity: A_{ef}, Cum A_{ef}, $\%f_{ef}$, and Cum $\%f_{ef}$. In Parts 1 and 2, the PK parameters for relevant metabolites of LOXO-292 may be calculated, as deemed appropriate, based on plasma, urine, and fecal concentration levels.
Sample Size:	The sample sizes chosen for Parts 1 and 2 of this study were based on precedent set by other AME and absolute bioavailability studies of similar nature and were not based on power calculations.
Statistical Methods:	For Parts 1 and 2, descriptive statistics (number of observations, arithmetic mean, standard deviation, 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.

2 INTRODUCTION[a]

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

2.1 Background

LOXO-292 is a small molecule selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase designed to competitively block the adenosine triphosphate binding site of the kinase. LOXO-292 was at least 250-fold more selective for RET than for 98% of 329 other kinases tested in a large in vitro screen. Consistent with such a high degree of selectivity, LOXO-292 caused significant inhibition of cell growth in human cancer cell lines that harbored endogenous, clinically relevant RET gene alterations but was much less inhibitory against human cancer cell lines without RET alterations. Potent and selective inhibition of RET may provide clinical benefit to subjects with malignancies due to oncogenic alterations in RET or with other mechanisms of increased RET activity.

2.2 Summary of Nonclinical Studies

Pharmacology safety of LOXO-292 was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-a-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented minipigs, and in a GLP 28-day repeat-dose toxicology study (with electrocardiogram [ECG] monitoring) in minipigs. LOXO-292 had a half maximal inhibitory concentration value (IC_{50}) of 1.1 µM in the GLP hERG assay, which is approximately 17- and 9-fold higher than the predicted maximum unbound concentration at the clinical dose of 80 mg and 160 mg, respectively, twice daily (BID). There were no LOXO-292-related changes in any cardiovascular endpoints including QT interval corrected for heart rate (QTc) at doses up to 12 mg/kg in the safety pharmacology cardiovascular study in conscious minipigs. Furthermore, there were no LOXO-292-related ECG changes in the 28-day repeat-dose toxicity study in minipigs at the high dose of 12 mg/kg. Together, these data indicate that LOXO-292 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

Administration of LOXO-292 at single doses up to 45 mg/kg in male rats had no effect on respiratory function.

[a] Information supplied by the Sponsor.

Potential effects of LOXO-292 on the central nervous system were evaluated as part of the GLP 28-day repeat-dose study in rats, in functional observational battery tests and locomotor activity assessments. Findings were limited to animals receiving the high dose on Week 4 of the dosing phase, and were attributed to poor general body condition and weight changes associated with LOXO-292 administration rather than specific neurological effects. Additionally, no microscopic abnormalities in neuronal tissues were found.

In toxicology studies of LOXO-292 that were conducted in the rat and minipig, the primary pathologic findings for both species were in the tongue, pancreas, bone marrow, and lymphoid tissues; while the gastrointestinal (GI) tract and ovaries were target tissues in minipig. Other target tissues identified in the rat included: multi-tissue mineralization, physeal cartilage, incisor teeth, lung, Brunner's gland, and possibly liver. Assessment of doses associated with moribundity/death revealed a steep dose response curve for both species.

LOXO-292 was not mutagenic in the GLP bacterial mutation assay. LOXO-292 was not found to be phototoxic when evaluated in an in vitro neutral red uptake phototoxicity assay.

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dosing regimens $\geq$ 40 mg/day.

Based on the nonclinical profile, including results from animal toxicology studies, theoretical risks of human exposure to LOXO-292 include the following: loss of appetite, decrease in body weight, increase in total white blood cells, neutrophils, and monocytes, decrease in albumin, increase in globulin, decreased albumin:globulin ratio, decrease in total protein, increased body temperature, lethargy, increase in cholesterol and triglycerides, increase in phosphorus, changes in taste sensation and/or development of xerostomia, GI symptoms/signs: nausea, vomiting, loose stools, abdominal discomfort, decreases in red cell mass (red blood cells, hemoglobin, hematocrit) and reticulocytes, decrease in platelets, increases in liver function tests (alkaline phosphatase [ALP], aspartate aminotransferase [AST], and alanine aminotransferase [ALT]).

LOXO-292 has been given orally and intravenously (IV) to mice, rats, dogs, minipigs, and monkey. LOXO-292 was absorbed and bioavailable in all species tested. Solubility studies and pharmacokinetic (PK) studies suggest that the PK exposure of LOXO-292 may be reduced by proton pump inhibitors and other antacids. LOXO-292 appears to be metabolized primarily by cytochrome P450 (CYP)3A4, but at therapeutically relevant exposures, it is not anticipated to inhibit or induce drug-metabolizing enzymes. LOXO-292 is also a substrate for breast cancer resistance protein transporter.

Refer to the IB[1] for detailed background information on LOXO-292.

2.3 Summary of Clinical Studies

LOXO-292 is currently being studied in an ongoing global Phase 1 first-in-human Study LOXO-RET-17001 in patients with advanced solid tumors including RET fusion-positive non-small cell lung cancer, RET-mutant medullary thyroid cancer, and other tumors with increased RET activity. The starting dose of LOXO-292 was CCI once daily. As of a January 5, 2018 data cut-off date, safety data were available from 57 patients with 160 mg BID as the highest dose administered. As of the January 5, 2018, no dose-limiting toxicities (DLTs) have been reported. Treatment-emergent AEs (TEAEs) occurring in ≥ 10% of patients were: fatigue (16%), diarrhea (16%), and dyspnea (12%). The majority of TEAEs were Grades 1 or 2 and no ≥ Grade 3 TEAEs were related to study drug. Three subjects have died during the study, and no deaths have been attributed to study drug.

Loxo Oncology has also initiated 3 Institutional Review Board (IRB)-approved, Food and Drug Administration (FDA)-allowed single patient protocols (LOXO-RET-17002, LOXO-RET-17003, and LOXO-RET-17004) to provide access to LOXO-292 for patients with clinical need not meeting eligibility criteria for the ongoing clinical studies. As of January 5, 2018, no TEAEs have been attributed to study drug for these patients.

As of February 9, 2018, PK data were available from patients (from the LOXO-RET-17001 study). LOXO-292 is absorbed after oral administration with a time to maximum observed concentration (T_{max}) of approximately 2 hours. Although the PK sampling of LOXO-292 was not long enough to adequately characterize area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0-\infty}$), the half-life was estimated to be at least 12 hours or longer. Low concentrations of LOXO-292 were recovered as unchanged drug in urine indicating that the kidney contributes to overall clearance.

Refer to the IB[1] for additional detailed background information on LOXO-292.

2.4 Study Rationale

In nonclinical studies, the metabolic profile of LOXO-292 has been studied in liver microsomes and hepatocytes from male CD-1 mice, male Sprague-Dawley rats, male beagle dogs, male Göttingen minipigs, and humans. Its excretion has been studied in minipigs. However, excretion pathways in humans have not been fully evaluated. In nonclinical PK studies, LOXO-292 was orally bioavailable in the mouse, rat, dog, monkey, and minipig. In clinical studies, preliminary PK data have shown that LOXO-292 is rapidly absorbed after oral administration. However, its absolute bioavailability in humans has not been determined. The present study will provide

additional data about the excretion profile and absolute bioavailability of LOXO-292 in healthy male subjects.

Part 1 is a standard mass balance study to determine the absorption, metabolism, and excretion (AME) kinetics of LOXO-292 and to determine and characterize metabolites present in plasma, urine, and feces in healthy male subjects following a single oral dose of 160 mg of [^{14}C]-LOXO-292 (containing ~40 µCi) administered as an oral solution. Blood, plasma, urine, and feces sampling will be conducted until at least Day 8 and potentially until Day 22. The duration of the study is considered adequate to achieve study objectives based on the known clinical PK of LOXO-292.

Part 2 uses an IV microtracer method to determine the absolute bioavailability of LOXO-292 following a single oral dose of 160 mg of LOXO-292 and an IV microtracer dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi). 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. Absolute bioavailability will be determined by comparing the plasma exposure of LOXO-292 following oral dosing with the plasma exposure of [^{14}C]-LOXO-292 following IV dosing. The IV dose of [^{14}C]-LOXO-292 will be administered so that peak plasma concentrations of [^{14}C]-LOXO-292 occur approximately at the T_{max} of LOXO-292 following oral dosing. Because it includes urine and feces sampling, Part 2 will also provide additional data about the excretion profile of LOXO-292. Analysis of urine concentrations of LOXO-292, [^{14}C]-LOXO-292, and total radioactivity will allow for the determination of renal clearance (CL_R) and the percentage of LOXO-292 excreted unchanged in the urine. Analysis of total radioactivity in fecal samples following IV dosing will provide information about the extent of fecal excretion of LOXO-292.

Female subjects will be excluded to align with regulatory guidance. The “as low as (is) reasonably achievable” (ALARA) principle prescribed by both the FDA and Nuclear Regulatory Commission (2007) 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 the study drug is different in females versus males), then the radiation exposure to female subjects should be kept at zero potential by not including females in radioactivity studies and only enrolling and dosing male subjects.

2.5 Dose Rationale

An oral dose has been selected for this study because this is the intended clinical route of administration. The nonradiolabeled dose of 160 mg of LOXO-292 was selected based on study objectives, clinical study results, and safety considerations. The 160-mg dose is expected to

ensure sufficient quantifiable plasma concentrations of LOXO-292 for determination of systemic PK. In a Phase 1 clinical study (LOXO-RET-17001), 160 mg of LOXO-292 dosed BID was well tolerated and no DLTs were determined; therefore, a single 160-mg dose is expected to be well tolerated. In summary, it is expected that a 160-mg dose will allow for achievement of the study objectives with minimal risk to subjects.

The planned radioactive dose of ~40 µCi (with an allowable maximum of 45 µCi) of [^{14}C]-LOXO-292 in Part 1 is expected to provide adequate levels of radioactivity to achieve the study objectives while minimizing the risk of excessive radiation exposure to healthy subjects. A quantitative whole body autoradiography study in male Long-Evans rats indicated that administration of 40 µCi will result in an overall human male whole-body exposure of approximately 322 mrem, which is well below the FDA-allowable exposure limit of 3000 mrem for single-dose isotope studies in humans, according to the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Subjects, Radioactive Drugs for Certain Research Uses (21 CFR 361.1). It is expected that the planned radioactive dose will provide a sufficient radioactive signal for total radioactivity counting and quantitative radioprofiling of [^{14}C]-LOXO-292 in blood, plasma, and excreta (urine and feces) with minimal radiation risk to subjects.

The radioactive dose of ~1 µCi of [^{14}C]-LOXO-292 in Part 2 is only about 1% 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 accelerator mass spectrometry (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.

3 STUDY OBJECTIVES

Part 1:

The primary objectives of Part 1 of this study are:

- To determine mass balance and routes of elimination of [^{14}C]-LOXO-292 following oral administration of a single 160-mg (~40 µCi) radiolabeled dose of LOXO-292 in healthy male subjects
- To assess the PK of a single dose of LOXO-292 using [^{14}C]-LOXO-292
- To determine the whole blood and plasma concentrations of total radioactivity
- To determine the urinary and fecal recovery of total radioactivity
- To characterize and identify metabolites of [^{14}C]-LOXO-292 in plasma, urine, and feces.

The secondary objective of Part 1 of this study is:

- To assess the safety and tolerability of [^{14}C]-LOXO-292 (containing ~40 µCi).

Part 2:

The primary objectives of Part 2 of this study are:

- To determine the absolute bioavailability of LOXO-292 following a single oral dose of 160 mg of LOXO-292 along with an IV dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi)
- To evaluate the PK of LOXO-292 following oral and IV dosing
- To evaluate the urinary excretion of LOXO-292 following oral dosing and of [^{14}C]-LOXO-292 following IV dosing
- To evaluate the fecal recovery of total radioactivity following IV dosing of [^{14}C]-LOXO-292.

The secondary objective of Part 2 of this study is:

- To assess the safety and tolerability of LOXO-292.

4 INVESTIGATIONAL PLAN

4.1 Study Design

This study will be an open-label, 2-part AME and absolute bioavailability study of [^{14}C]-LOXO-292. 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 kinetics of LOXO-292, to identify and characterize metabolites of LOXO-292, and to assess the safety and tolerability of [^{14}C]-LOXO-292. Subjects in Part 1 will be administered a single oral dose of 160 mg of [^{14}C]-LOXO-292 (containing ~40 µCi) as an oral solution. In order to complete 6 subjects, 6 will be enrolled (different subjects from those participating in Part 2), along with 2 alternates (to be dosed in the event that dosing is unsuccessful for any of the initial 6 subjects). In the event of early withdrawal of any subjects after the alternate subjects are released, replacement subjects may be enrolled at the discretion of the Sponsor.

Part 2 is designed to determine the absolute bioavailability of LOXO-292, to evaluate the urinary excretion of LOXO-292 and [^{14}C]-LOXO-292, to evaluate the fecal excretion of [^{14}C]-LOXO-292, and to assess the safety and tolerability of LOXO-292. Subjects in Part 2 will be administered a single oral dose of 160 mg of LOXO-292 as 2 x 80-mg capsules followed

2 hours later by a single dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi) administered as an IV push over approximately 2 minutes. In order to complete 6 subjects, 6 will be enrolled (different subjects from those participating in Part 1), along with 2 alternates (to be dosed in the event that dosing is unsuccessful for any of the initial 6 subjects). In the event of early withdrawal of any subjects after the alternate subjects are released, 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 LOXO-292, [^{14}C]-LOXO-292 (Part 2 only), total radioactivity, and metabolite (Part 1 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 Safety Follow-up Call. The planned duration of study conduct for Part 1 is up to 59 days from Screening through the Safety Follow-up Call. The planned duration of study conduct for Part 2 is up to 46 days from Screening through the Safety Follow-up Call.

A schematic of the study design of Part 1 is presented in Figure 4-1 and a schematic of the study design of Part 2 is presented in Figure 4-2.

Figure 4-1 Study Design Schematic: Part 1

Screening	Check-in	Dosing[a]	LOXO-292 and Total Radioactivity Concentrations, and MetID Sampling	Clinic Discharge[b]	Safety Follow-up Call[c]
Days -29 to -2	Day -1	Day 1	Day 1 to Clinic Discharge	Days 8 to 22	Approximately 7 days after Clinic Discharge
	Clinic Confinement				

MetID = metabolite profiling and identification

[a] Single oral dose of 160 mg of [^{14}C]-LOXO-292 (~40 µCi) administered as an oral solution following an overnight fast.

[b] Subjects will be discharged from the Clinical Research Unit (CRU) starting on Day 8 if ≥ 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 8, subjects will continue to be confined in the CRU until these criteria are met, up to a maximum of Day 22.

[c] Subjects will receive a Safety Follow-up Call approximately 7 days after Clinic Discharge.

Figure 4-2 Study Design Schematic: Part 2

Screening	Check-in	Dosing[a]	LOXO-292, [^{14}C]-LOXO-292, and Total Radioactivity Concentrations	Clinic Discharge	Safety Follow-up Call[b]
Days -29 to -2	Day -1	Day 1	Day 1 to Day 9	Day 9	Approximately 7 days after Clinic Discharge
	Clinic Confinement				

[a] Single oral dose of 160 mg of LOXO-292 administered as 2 x 80-mg capsules following an overnight fast. A single intravenous (IV) dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi of radioactivity) will be administered by IV push 2 hours after the oral dose.
[b] Subjects will receive a Safety Follow-up Call approximately 7 days after Clinic 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 8 hours, subjects will receive a single oral dose of 160 mg of [^{14}C]-LOXO-292 (containing ~40 µCi) administered as an oral solution. Subjects will be confined at the CRU from the time of Check-in until Clinic Discharge (between Days 8 and 22). After completing discharge procedures, subjects will be discharged from the CRU as early as Day 8 and up to Day 22, provided recovery of radioactivity has reached the following threshold values:

- ≥ 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 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.

Safety will be monitored with AE inquiries, clinical laboratory evaluations (Appendix A), vital signs measurements, 12-lead ECGs, and physical examinations during the study.

Samples for determination of LOXO-292 concentrations in plasma, total radioactivity concentrations in plasma, whole blood, urine, and feces, and for metabolite profiling/characterization will be obtained through at least 168 hours postdose (Day 8), and possibly up to 504 hours postdose (Day 22). A Schedule of Assessments for Part 1 is presented in Table 6-1.

In Part 1, for subjects experiencing emesis within 2 hours following dosing, vomitus will be collected. That subject may be considered not evaluable and 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.

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 8 hours, subjects will receive a single oral dose of 160 mg of LOXO-292 as 2 x 80-mg capsules followed 2 hours later by a single dose of < 100 µg of [^{14}C]-LOXO-292 (containing ~1 µCi) administered as an IV push over approximately 2 minutes. Subjects will be confined at the CRU from the time of Check-in until Day 9 and will be discharged from the CRU after completing all discharge procedures. Subjects will receive a Safety Follow-up Call approximately 7 days after Clinic Discharge.

As in Part 1, safety will be monitored with AE inquiries, clinical laboratory evaluations (Appendix A), vital signs measurements, 12-lead ECGs, and physical examinations during the study.

Samples for determination of plasma and urine concentrations of LOXO-292 and [^{14}C]-LOXO-292 and for determination of total radioactivity concentrations in urine and feces will be obtained through 192 hours postdose (Day 9). A Schedule of Assessments for Part 2 is presented in Table 6-2.

4.2 Discussion of Study Design

Part 1 of this study is designed to characterize the AME kinetics of LOXO-292 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-292 that are produced following oral dosing.

Part 2 is designed to determine the absolute bioavailability of LOXO-292 by comparing its plasma exposure following oral dosing to the plasma exposure of [^{14}C]-LOXO-292 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-292 will be administered so that peak plasma concentrations of [^{14}C]-LOXO-292 occur approximately at the T_{max} of LOXO-292 following oral dosing.

Analysis of urine concentrations of LOXO-292, [^{14}C]-LOXO-292, and total radioactivity will allow for determination of CL_R and for the percentage of LOXO-292 excreted unchanged in urine. Analysis of total radioactivity in feces will provide information about the extent of fecal excretion of LOXO-292.

In Part 2, a microtracer (~1 μCi) of [^{14}C]-LOXO-292 will be used. This low level of radioactivity necessitates the use of 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). Conducting the study in healthy subjects will allow the evaluation of LOXO-292 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.

5 SUBJECT SELECTION

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 Investigator's (or designee's) discretion.

Each subject is allowed to participate in only one part of the study. In order to complete 6 subjects in each part of the study, 6 subjects and 2 alternates will be enrolled in Parts 1 and 2. The alternates will be dosed only in the event that dosing is unsuccessful for any of the initial 6 subjects. In the event of early withdrawal of any subjects after the alternate subjects are released, replacement subjects may be enrolled at the discretion of the Sponsor.

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).

5.1 Inclusion Criteria

Subjects who meet the following criteria at Screening and Check-in may be included in the study:

1. Males of any race between 18 and 55 years of age, inclusive, at Screening
2. Body mass index between 18.5 and 32.0 kg/m^2, inclusive, at Screening
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, or clinical

laboratory evaluations (Appendix A) at Screening or Check-in as assessed by the Investigator (or designee)

4. Subjects will be surgically sterile for at least 90 days prior to Check-in or, when sexually active with female partners of childbearing potential, will agree to use effective contraception methods, as detailed in Section 6.3.3, or abstain from sexual intercourse from the time of first dose through 6 months after study drug administration. Subjects must agree not to donate sperm from Check-in until 6 months after the last dose of study drug
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions
6. History of having a minimum of 1 bowel movement per day.

5.2 Exclusion Criteria

The following will exclude potential subjects from the study:

1. Significant history or clinical manifestation of any metabolic, allergic, infectious, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, GI, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee)
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee)
3. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed)
4. History of congenital nonhemolytic hyperbilirubinemia (eg, Gilbert's syndrome)
5. Has had a cholecystectomy
6. History of alcoholism or drug/chemical abuse within 2 years prior to Check-in
7. Typical alcohol consumption of > 21 units per week for males. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL wine)
8. Positive urine drug screen (including cotinine) at Screening, or positive urine drug screen (including cotinine) or alcohol breath test at Check-in
9. Positive hepatitis panel and/or positive human immunodeficiency virus (HIV) test (Appendix A). Subjects whose results are compatible with prior immunization and not infection may be included at the discretion of the Investigator (or designee)

10. Estimated creatinine clearance < 90 mL/min at Screening or Check-in, calculated using the Cockcroft-Gault equation
11. Abnormal liver function tests (LFTs), as defined by AST, ALT, ALP, 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, unless deemed acceptable by the Investigator (or designee) with prior Sponsor approval. Rechecks of LFTs 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 LFT values if the Investigator and the Sponsor deem that the results are not clinically significant and will not impact study conduct.
12. Supine systolic blood pressure (BP) is < 89 mmHg or > 139 mmHg, or supine diastolic BP is < 50 mmHg or > 89 mmHg, at Screening, Check-in, or prior to dosing on Day 1 of Part 1 or Part 2, unless deemed acceptable by the Investigator (or designee) with prior Sponsor approval. Rechecks of 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 BP values if the Investigator and the Sponsor deem that the results are not clinically significant and will not impact study conduct.
13. Supine heart rate is < 50 bpm or > 99 bpm at Screening or Check-in, unless deemed acceptable by the Investigator (or designee) with prior Sponsor approval. Rechecks of heart rate will be permitted up to 2 times to confirm eligibility for study participation. Subjects may be eligible for participation in the study based on rechecked heart rates if the Investigator and/or the Sponsor deem that the results are not clinically significant and will not impact study conduct.
14. Cardiac exclusions: History or presence of any of the following, deemed clinically significant by the Investigator (or designee) and/or Sponsor:
    - history or presence of clinically significant cardiovascular disease:
        - myocardial infarction or cerebrovascular thromboembolism within 6 months prior to first dosing
        - symptomatic angina pectoris
        - New York Heart Association Class ≥ 2 congestive heart failure
        - congenital prolonged QT syndrome
        - ventricular pre-excitation syndrome (Wolff-Parkinson White syndrome)
        - arrhythmia (excluding benign sinus arrhythmia) or history of arrhythmia requiring medical intervention
        - ventricular dysfunction or risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, family history of Long QT Syndrome)

        - significant screening ECG abnormalities:
            - Left bundle-branch block
            - Second degree atrioventricular (AV) block, type 2, or third degree AV block
            - QT interval corrected for heart rate using Fridericia's method (QTcF) is > 450 msec
    - ECG findings deemed abnormal with clinical significance by the Investigator (or designee) at Screening or Check-in

15. Participation in any other radiolabeled investigational study drug trial within 12 months prior to Check-in. Any previous radiolabeled study drug must have been received more than 12 months prior to Check-in for this study
16. Exposure to significant radiation (eg, serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring) within 12 months prior to Check-in
17. 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 Check-in
18. Use or intention to use any medications/products known to alter drug AME processes, in particular strong inducers or inhibitors of CYP3A4 enzymes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee)
19. Use or intention to use any prescription medications/products within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee)
20. Use or intention to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee)
21. Use or intention to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee)
22. Consumption of foods and beverages containing poppy seeds, grapefruit, or Seville oranges from 7 days prior to Check-in
23. Consumption of alcohol-, caffeine-, or xanthine-containing foods and beverages from 72 hours prior to Check-in, unless deemed acceptable by the Investigator (or designee)
24. Strenuous exercise within 48 hours prior to Check-in
25. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in

26. Receipt of blood products within 2 months prior to Check-in
27. Donation of blood from 56 days prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening
28. Poor peripheral venous access
29. Have previously completed or withdrawn from any other study investigating LOXO-292, and have previously received the investigational product
30. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

5.3 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) or Sponsor may remove a subject from the study if, in the Investigator's (or designee's) or Sponsor's opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn due to the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, intake of nonpermitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of withdrawal will immediately be made to the Sponsor's Study Monitor. In case of withdrawal of study participation, efforts will be made to perform all final study day assessments (Table 6-1 and Table 6-2). 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 will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

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

- AEs not previously observed following administration of LOXO-292 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
- discontinuation of clinical development of LOXO-292.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

A Schedule of Assessments for Part 1 is presented in Table 6-1. A Schedule of Assessments for Part 2 is presented in Table 6-2. The total blood volume that will be taken during the study is outlined in Appendix B.

Table 6-1 Schedule of Assessments: Part 1

	Screening	Check-in	Treatment							Check-out	Follow-up
Events	**Days -29 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Clinic Discharge [a] (Days 8 to 22)/ET [b]**	**Safety Follow-up Call (approximately 7 days after Clinic Discharge)**
Informed Consent	X										
Assignment of Screening Number	X										
Review of Inclusion/Exclusion Criteria	X	X									
Demographic Data	X										
Medical History [c]	X	X									
Prior Medications	X	X									
Height, Weight, BMI Calculation [d]	X	X									
Alcohol and Drug Screen [e]	X	X									
Serology Test (HBcAb, HBsAg, HCV Ab, HIV)	X										
Confinement to CRU		X	X	X	X	X	X	X	X	X	
Assignment of Subject Number			X								
Physical Examination [f]	X	X								X	
Clinical Laboratory Safety Tests (clinical chemistry, TSH [Screening only], hematology, and urinalysis) [g]	X	X				X				X	

	Screening	Check-in	Treatment							Check-out	Follow-up
Events	**Days -29 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Clinic Discharge [a] (Days 8 to 22)/ET [b]**	**Safety Follow-up Call (approximately 7 days after Clinic Discharge)**
Vital Signs (oral temperature, BP, heart rate, and respiratory rate) [h]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG [i]	X	X	X							X	
LOXO-292 Administration (LOXO-292 160 mg/~40 µCi [^{14}C]-LOXO-292)			X								
CCI											
AE, SAE, and Concomitant Medications and Procedures Monitoring and Recording [a]	X----------Ongoing----------X										

AE = adverse event; BMI = body mass index; BP = blood pressure; CRU = Clinical Research Unit; ECG = electrocardiogram; ET = early termination; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

[a] Subjects may be discharged from the CRU starting on Day 8 if ≥ 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 8, subjects will continue to be confined in the CRU until these criteria are met, up to a maximum of Day 22.
[b] Subjects who withdraw from the study prior to meeting discharge criteria should undergo all discharge tests and assessments at ET, and will receive a Safety Follow-up Call approximately 7 days after ET.
[c] A full medical history will be recorded at Screening. An interim medical history update will be recorded on Day -1.
[d] Height and BMI will be measured at Screening only.
[e] Drug urine screen (which includes cotinine) will be conducted at Screening and at Check-in (Day -1). An alcohol breath test will be conducted at Check-in only.
[f] A complete physical examination will be conducted at Screening and at Clinic Discharge/ET. An abbreviated physical examination (general, heart, lungs, abdomen, and skin) will be conducted at Check-in.
[g] Every attempt will be made to ensure blood samples for the clinical chemistry panel are collected following a fast from food for at least 8 hours. Test for TSH will be performed at Screening only. Other clinical laboratory evaluations will be conducted at Screening, Check-in, on Day 4, and at Clinic Discharge/ET.
[h] Subjects are to remain supine for at least 5 minutes prior to vital signs measurements. Vital signs will be obtained at Screening; Check-in; on Day 1 predose and 2 hours postdose; and daily (24-hour intervals) up to and including day of Clinic Discharge/ET. When scheduled at the same nominal times, postdose vital signs measurements are to be performed prior to postdose PK blood draws (see Section 6.5), with blood draws occurring as close to the nominal times as possible.
[i] Subjects are to remain supine for at least 5 minutes prior to ECG assessments. The ECGs will be obtained at Screening and Check-in, on Day 1 predose, 2 hours postdose, and at Clinic Discharge/ET. When scheduled at the same nominal times, postdose ECGs are to be performed prior to postdose vital signs measurements and PK blood draws (see Section 6.5), with blood draws occurring as close as possible to the nominal times.
[j] CCI [redacted]
[n] AEs, SAEs, and concomitant medications and procedures will be monitored and recorded throughout the study from the time of signing the informed consent, as described in Section 6.5.1, Appendix C, and Section 6.3.2. A "How Do You Feel?" AE inquiry will be performed at Screening, Check-in, each vital signs measurement, and during the Safety Follow-up Call.

Table 6-2 Schedule of Assessments: Part 2

	Screening	Check-in	Treatment								Check-out	Follow-up
Events	**Days -29 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Clinic Discharge or ET [a] Day 9**	**Safety Follow-up Call (approximately 7 days after Clinic Discharge)**
Informed Consent	X											
Assignment of Screening Number	X											
Review of Inclusion/Exclusion Criteria	X	X										
Demographic Data	X											
Medical History [b]	X	X										
Prior Medications	X	X										
Height, Weight, BMI Calculation [c]	X	X										
Alcohol and Drug Screen [d]	X	X										
Serology Test (HBcAb, HBsAg, HCV Ab, HIV)	X											
Confinement to CRU		X	X	X	X	X	X	X	X	X	X	
Assignment of Subject Number			X									
Physical Examination [e]	X	X									X	
Clinical Laboratory Evaluations (clinical chemistry TSH [Screening only], hematology, urinalysis) [f]	X	X				X					X	

	Screening	Check-in	Treatment								Check-out	Follow-up
Events	**Days -29 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Clinic Discharge or ET [a] Day 9**	**Safety Follow-up Call (approximately 7 days after Clinic Discharge)**
Vital Signs (oral temperature, BP, heart rate, and respiratory rate) [g]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG [h]	X	X	X								X	
Oral LOXO-292 160 mg Administration [i]			X									
IV [^{14}C]-LOXO-292, < 100 µg (~1 µCi) Administration [i]			X									
CCI												
AE, SAE, and Concomitant Medications and Procedures Monitoring and Recording [m]	X----------Ongoing----------X											

AE = adverse event; BMI = body mass index; BP = blood pressure; CRU = Clinical Research Unit; ECG = electrocardiogram; ET = early termination; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; IV = intravenous; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

[a] Subjects who withdraw from the study prior to Day 9 should undergo all discharge tests and assessments at ET, and will receive a Safety Follow-up Call approximately 7 days after ET.
[b] A full medical history will be recorded at Screening. An interim medical history update will be recorded on Day -1.
[c] Height and BMI will be measured at Screening only.
[d] Drug urine screen (which includes cotinine) will be conducted at Screening and at Check-in (Day -1). An alcohol breath test will be conducted at Check-in only.
[e] A complete physical examination will be conducted at Screening and at Clinic Discharge/ET. An abbreviated physical examination (general, heart, lungs, abdomen, and skin) will be conducted at Check-in.
[f] Every attempt will be made to ensure blood samples for the clinical chemistry panel are collected following a fast from food for at least 8 hours. Test for TSH will be performed at Screening only. Other clinical laboratory evaluations will be conducted at Screening, Check-in, on Day 4, and at Clinic Discharge/ET.
[g] Subjects are to remain supine for at least 5 minutes prior to vital signs measurements. Vital signs will be obtained at Screening; Check-in; on Day 1 predose, at 2 hours postdose relative to oral dose administration; and daily (24-hour intervals) up to and including day of Clinic Discharge/ET. When scheduled at the same nominal times, postdose vital signs measurements are to be performed prior to postdose PK blood draws (see Section 6.5), with blood draws occurring as close to the nominal times as possible.
[h] Subjects are to remain supine for at least 5 minutes prior to ECG assessments. The ECGs will be obtained at Screening and Check-in, on Day 1 predose and 2 hours postdose relative to oral dose administration, and at Clinic Discharge/ET. When scheduled at the same nominal times, postdose ECGs are to be performed prior to postdose vital signs measurements and PK blood draws (see Section 6.5), with blood draws occurring as close to the nominal times as possible.
[i] See Section 4.1 for dosing details.
[j] CCI [redacted]
[m] AEs, SAEs, and concomitant medications and procedures will be monitored and recorded throughout the study from the time of signing the informed consent, as described in Section 6.5.1, Appendix C, and Section 6.3.2. A "How Do You Feel?" AE inquiry will be performed at Screening, Check-in, each vital signs measurement, and during the Safety Follow-up Call.

6.2 Study Treatment

6.2.1 Drug Supplies and Accountability

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drugs for Part 1 (Table 6-3) and Part 2 (Table 6-4). For Part 1, nonradiolabeled LOXO-292 (provided as a powder) and [^{14}C]-LOXO-292 (provided as a solid) will be formulated by Covance to the desired concentration in order to achieve the final oral dose solution (~40 µCi/160 mg per subject). For the oral dose portion of Part 2, nonradiolabeled LOXO-292 will be supplied by the Sponsor as 2 x 80-mg capsules. For the IV dose portion of Part 2, [^{14}C]-LOXO-292 (provided as a solid) will be formulated by Covance in order to achieve the final IV dose solution (~1 µCi/< 100 µg per subject).

Table 6-3 Supplied Study Drugs: Part 1

Study Drug	[^{14}C]-LOXO-292	LOXO-292
Form[a]	Solid	Powder
Strength	N/A	N/A
Specific Activity	~100 µCi/mg	N/A
Supplier	Loxo Oncology, Inc.	Loxo Oncology, Inc.
Manufacturer	Selcia, Ltd.	Avista Pharma Solutions, Inc.

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

Table 6-4 Supplied Study Drugs: Part 2

Study Drug	LOXO-292	[^{14}C]-LOXO-292
Form[a]	Oral Capsule	Solid
Strength	80 mg	N/A
Specific Activity	N/A	~100 µCi/mg
Supplier	Loxo Oncology, Inc.	Loxo Oncology, Inc.
Manufacturer	Avista Pharma Solutions, Inc.	Selcia, Ltd.

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

The lot numbers (or equivalent) for the study drugs will be provided to the CRU by the supplier/manufacturer when supplies are shipped.

Nonradiolabeled study drug capsules will be stored at room temperature (between 15°C and 30°C) under secure conditions. Nonradiolabeled study drug powder will be stored at room temperature (between 15°C and 30°C) under secure conditions. Radiolabeled study drug will be stored frozen as indicated on the product label and/or Certificate of Analysis (or equivalent).

The Investigator (or designee) will maintain an accurate record of the receipt of the clinical trial materials as shipped by the Sponsor (or designee), including the date received. One copy of this receipt will be returned to the Sponsor when the contents of the shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. 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 on request.

At the completion of the study, all unused drug supplies will be returned to the Sponsor (or designee) or disposed of by the CRU per the Sponsor's (or designee's) written instructions.

6.2.2 Subject Number and Identification

After signing the ICF, subjects will be assigned a unique screening number by the study site. Subjects will be assigned a subject number at the time of the first dosing occasion. Assignment of numbers will be in ascending order and no numbers will be omitted. Subject numbers will be used on all study documentation. For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. Replacement subjects will be assigned a subject number by adding 100 to the number of the subject they are replacing (eg, Subject No. 105 replaces Subject No. 005).

6.2.3 Dose Preparation and Administration

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.

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

Appropriate unit doses, as described above, will be administered to consecutively-numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at specific times, the exact dose time of consecutive 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 eCRFs.

Each oral dose will be administered orally with approximately 240 mL room temperature water. A hand and mouth check will be performed to verify that the dose administered was swallowed. Oral doses will be preceded by an overnight fast (ie, at least 8 hours) from food (not including

water) and will be followed by a fast from food (not including water) for at least 4 hours postdose. Except as part of dose administration, subjects will restrict their consumption of water for 1 hour predose and for 2 hours postdose; at all other times during the study, subjects may consume water ad libitum.

Except when they are using the toilet, study subjects will be observed for approximately 4 hours postdose. Subjects will not lay supine for 1 hour following each dose administered, except as necessitated by the occurrence of an AE(s) and/or study procedures.

6.2.4 Blinding

This is an open-label study.

6.3 Study Restrictions

6.3.1 Diet, Fluid, and Activity Control

Subjects are required to refrain from use of tobacco- or nicotine-containing products within 3 months prior to Check-in until Clinic Discharge.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until Clinic Discharge.

Subjects are required to abstain from consuming alcohol-, caffeine-, or xanthine-containing foods and beverages from 72 hours prior to Check-in until Clinic Discharge, unless deemed acceptable by the Investigator (or designee).

Subjects will refrain from strenuous exercise from 48 hours prior to Check-in and during the period of confinement at the CRU and will otherwise maintain their normal level of physical activity throughout the entire study (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion).

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.

6.3.2 Concomitant Medications

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

Subjects will refrain from the use of any medications/products known to alter drug AME processes, in particular strong inducers or inhibitors of CYP3A4, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).

Subjects will also refrain from the use of any prescription medications/products during the interval from 14 days prior to Check-in through Clinic Discharge, unless deemed acceptable by the Investigator (or designee). In addition, subjects will refrain from the use of any over-the-counter nonprescription medications (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) from 7 days prior to Check-in through Clinic Discharge, unless deemed acceptable by the Investigator (or designee).

Pitted prunes or prune juice may be used to help with bowel movements if necessary. Up to 2 grams per day of acetaminophen may be administered if approved by the Investigator (or designee). The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the study and the reason for its use will be documented in the source documents and the eCRF.

6.3.3 Contraception

Males who are capable of fathering a child must agree to use one of the following effective methods of contraception or abstain from sexual intercourse from the time of the first dose through 6 months after study drug administration:

- Male sterilization, with documented confirmation of surgical success. Male subjects will be surgically sterile for at least 90 days prior to Check-in. If documentation is not available, male subjects must follow the contraception methods below:
    - Male condom with spermicide, and
    - For female partner of male study participant:
        - intrauterine device (IUD; hormonal IUD; eg, Mirena®). Copper IUDs are acceptable (eg, ParaGard®);
        - established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation;
        - bilateral tubal ligation; or

- sponge, cervical cap, or diaphragm (barrier method).

Subjects who practice true abstinence because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner of a male subject) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described above.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms with spermicide are used from the time of the first dose until 6 months after the last dose of study drug. Male subjects are required to refrain from donation of sperm from Check-in until 6 months after the last dose of study drug.

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

6.4 Pharmacokinetic, [^{14}C] Radioactivity, and Metabolite Procedures

6.4.1 Pharmacokinetic, [^{14}C] Radioactivity, and Metabolite Blood Sample Collection

Part 1:
Blood samples for LOXO-292 analysis, total radioactivity, and metabolite profiling/characterization will be collected via direct venipuncture. Blood samples will be collected at the timepoints specified in Table 6-1.

Part 2:
Blood samples for determination of LOXO-292 and [^{14}C]-LOXO-292 plasma concentrations will be collected via direct venipuncture. Blood samples will be collected at the timepoints specified in Table 6-2.

Processing, storage, and shipping instructions for these blood samples will be presented in a separate document.

6.4.2 Pharmacokinetic, [^{14}C] Radioactivity, and Metabolite Urine Sample Collection

Part 1:
Urine samples for total radioactivity concentrations and metabolite profiling/characterization will be collected at the time intervals specified in Table 6-1.

Part 2:
Urine samples for determination of LOXO-292, [^{14}C]-LOXO-292, and total radioactivity concentrations will be collected at the time intervals specified in Table 6-2.

Processing, storage, and shipping instructions for these urine samples will be presented in a separate document.

6.4.3 [^{14}C] Radioactivity and Metabolite Fecal Sample Collection

Part 1:
Fecal samples for total radioactivity concentrations and metabolite profiling/characterization will be collected at the time intervals specified in Table 6-1. 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.

Part 2:
Fecal samples for determination of total radioactivity concentrations will be collected at the time intervals specified in Table 6-2. 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.

Processing, storage, and shipping instructions for these fecal samples will be presented in a separate document.

6.4.4 Emesis Sample Collection

In Part 1, for subjects experiencing emesis within 2 hours following dosing, vomitus will be collected. All vomitus collected will be stored for possible analysis. The time and date of collection will be recorded on the subject's source documents and eCRF. Vomitus will be analyzed as deemed appropriate.

6.4.5 Analytical Methodology

In Part 1, concentrations of total radioactivity will be determined in whole blood, plasma, urine, and feces using liquid scintillation counting (LSC). Plasma concentrations of LOXO-292 will be determined using a validated bioanalytical method. Profiling and characterization of metabolites in plasma, urine, and feces will be conducted using standard laboratory procedures.

In Part 2, concentrations of total radioactivity in urine and feces will be determined using AMS and/or LSC. Plasma and urine concentrations of [^{14}C]-LOXO-292 will be determined using high performance liquid chromatography fractionation followed by AMS analysis. Plasma and urine concentrations of LOXO-292 will be determined using a validated bioanalytical method.

Specifics of the analytical methods will be provided in a separate document.

6.5 Safety Procedures

Safety evaluations may be repeated at the Investigator's (or designee's) discretion.

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 the other procedures to be performed at the same timepoint. Except for at Screening and Check-in, the order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- Dosing
- Postdose PK blood sampling (which includes LOXO-292, [^{14}C]-LOXO-292 [Part 2 only], and total radioactivity concentrations, and metabolite profiling/characterization [Part 1 only])
- Start and end of urine and fecal collections (for drug assay)
- Vital signs measurements
- ECGs
- Blood and urine samples for clinical laboratories
- Physical examinations.

6.5.1 Adverse Events

Adverse event definitions; assignment of severity, causality, action taken, and outcome; and procedures for reporting serious AEs (SAEs) are detailed in Appendix C.

The condition of each subject will be monitored from time of signing the ICF to Clinic Discharge. In addition, subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How do you feel?" or "How have you been feeling since you were last asked?", as specified in Table 6-1 and Table 6-2, to assess for the occurrence of AEs. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All AEs, whether volunteered, identified by the subject's responses to How Do You Feel? inquiries, or noted on laboratory tests, vital signs measurements, ECGs, or physical examinations, will be recorded throughout the study (ie, from signing of the ICF until Study Completion), either as subject medical history (if the event is nonserious and reported prior to dosing) or as AEs (if serious or the event occurs after administration of LOXO-292). The nature, time of onset, duration, and severity will be documented, together with an Investigator's (or

designee's) opinion of the relationship to study drug. Adverse events recorded during the course of the study will be followed up, where possible, until they have resolved or become stable. This will be completed at the Investigator's (or designee's) discretion.

Subjects will receive a Safety Follow-up Call approximately 7 days after they are discharged from the CRU to determine if any AE has occurred since the last study visit.

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

Since the safety profile of LOXO-292 in humans has not been fully established, all SAEs related to LOXO-292 will be considered unexpected and reported as suspected unexpected serious adverse reactions.

6.5.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations (including clinical chemistry panel [should be fasted at least 8 hours], thyroid-stimulating hormone [Screening only], hematology, and urinalysis; Appendix A) will be collected at the timepoints specified in Table 6-1 and Table 6-2.

Screens for a hepatitis panel and HIV antibody will be performed at Screening. A drug screen for selected drugs of abuse, including cotinine (not including alcohol), will be performed at Screening and repeated (including alcohol) at Check-in.

6.5.3 Vital Signs

Vital signs measurements (including oral temperature, BP, heart rate, and respiratory rate) will be obtained at the timepoints specified in Table 6-1 and Table 6-2. Vital signs will be measured after the subject has been supine for at least 5 minutes.

6.5.4 Twelve-lead Electrocardiograms

A 12-lead ECG will be obtained at the timepoints specified in Table 6-1 and Table 6-2. Subjects will be supine for at least 5 minutes prior to obtaining an ECG measurement.

The ECG parameters (including heart rate; PR, QRS, and QT intervals; and QTcF) and the Investigator's (or designee's) overall interpretation of the ECG will be recorded in the eCRF.

6.5.5 Physical Examinations

Complete physical examinations and abbreviated physical examination (general, heart, lungs, abdomen, and skin) will be performed at the timepoints specified in Table 6-1 and Table 6-2. The time and date of the physical examination will be recorded in the eCRF and any clinically significant findings will be recorded as AEs.

7 DATA ANALYSES AND SAMPLE SIZE

7.1 Sample Size

The sample sizes chosen for Parts 1 and 2 of this study were based on precedent set by other AME and absolute bioavailability studies of similar nature and were not based on power calculations.

7.2 Study Populations

The PK Populations for Parts 1 and 2 will consist of all subjects who received at least 1 dose of study drug and have evaluable PK data.

The Safety Population will consist of all subjects who received at least 1 dose of study drug.

The All Subject Population will consist of any subjects who enrolled on to the study (signed informed consent).

7.3 Pharmacokinetic Analysis

Part 1:

Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of LOXO-292 and the whole blood and plasma concentrations of total radioactivity, according to the model independent approach.

C_{max}	maximum observed concentration
T_{max}	time to maximum observed concentration
AUC_{last}	AUC from time 0 to the time of the last quantifiable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{last} + (C_{last} \div \lambda_z)$

	where C_{last} is the last quantifiable concentration and λ_z is the apparent terminal elimination rate constant
λ_z	apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus-time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (2)/λ_z
CL/F	apparent systemic clearance (for LOXO-292 only)
V_z/F	apparent volume of distribution during the terminal phase (for LOXO-292 only)

Blood/Plasma AUC Ratio

$AUC_{0-\infty}$ of total radioactivity in whole blood/$AUC_{0-\infty}$ of total radioactivity in plasma

Plasma LOXO-292 /Total Radioactivity AUC Ratio

$AUC_{0-\infty}$ of LOXO-292 in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma.

Additionally, blood-to-plasma ratios at each sampling timepoint will be calculated to determine partitioning of total radioactivity into red blood cells.

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

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

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

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

Part 2:

Oral dose PK: Whenever possible, the following PK parameters will be calculated for each subject, based on the plasma concentrations of LOXO-292:

C_{max}	maximum observed concentration
T_{max}	time to maximum observed concentration
AUC_{last}	AUC from time 0 to the time of the last quantifiable concentration
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated as described above
λ_z	apparent terminal elimination rate constant
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (2)/λ_z
F	absolute bioavailability, calculated using the formula: $F = \frac{AUC_{0-\infty}\text{ (oral)} \times \text{Dose (IV)}}{AUC_{0-\infty}\text{ (IV)} \times \text{Dose (oral)}}$
CL/F	apparent systemic clearance
V_z/F	apparent volume of distribution during the terminal phase.

Intravenous dose PK: For each subject, the following PK parameters will be calculated whenever possible, based on the plasma concentrations of [^{14}C]-LOXO-292:

C_{max}	maximum observed concentration
T_{max}	time to maximum observed concentration
AUC_{last}	AUC from time 0 to the time of the last quantifiable concentration
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated as described above
λ_z	apparent terminal elimination rate constant
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (2)/λ_z
CL	systemic clearance
V_z	volume of distribution during the terminal phase
V_{ss}	volume of distribution at steady state.

In addition, for each subject, the following PK parameters will be calculated whenever possible, based on the urine concentrations of LOXO-292, [^{14}C]-LOXO-292, and total radioactivity:

A_{eu}	amount excreted in urine per sampling interval
Cum A_{eu}	cumulative amount excreted in urine
CL_R	renal clearance (LOXO-292 and [^{14}C]-LOXO-292 only), where $CL_R = A_{eu}/AUC$ $AUC_{0-\infty}$ may be used, if appropriate
$\%f_{eu}$	percentage of dose excreted in urine per sampling interval, where $\%f_{eu} = 100\ (A_{eu}/\text{dose})$

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

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix™ WinNonlin® Version 6.4 or higher (Certara USA Inc.).

Pharmacokinetic parameters for relevant metabolites of LOXO-292 may be calculated in Part 1 and/or Part 2, as deemed appropriate, based on plasma, urine, and/or fecal concentration levels.

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. Other data handling procedures will be detailed in the SAP.

7.4 Statistical Analysis of Pharmacokinetic Data

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

Specification of PK parameters for analysis; procedures for accounting for missing, unused, or spurious data; procedures for reporting deviations from the original statistical plan; and selection of subjects to be included in the analyses population(s), as applicable, will be presented in the Clinical Study Report and/or SAP as appropriate.

7.5 Statistical Analyses of Safety Data

For Parts 1 and 2, descriptive statistics will be calculated on the safety parameters. No formal statistical analyses are planned.

All AEs will be coded by the Medical Dictionary for Regulatory Activities (Version 20.0 or higher). Each sign or symptom reported will be graded on the National Institution of Health's

Common Terminology Criteria for Adverse Events Version 5.0 (or higher) toxicity grading scale as referenced in Appendix C . The number (%) of subjects with any AE will be summarized by system organ class and preferred term. Descriptive statistics will be provided for clinical laboratory values, vital signs, and ECGs. Concomitant medications will be listed and coded according to the World Health Organization Drug Dictionary (September 2015 or later). Additional details will be provided in the SAP.

7.6 Data Handling and Record Keeping

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

7.7 Quality Control and Quality Assurance

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

8 ADMINISTRATIVE ASPECTS

8.1 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).

8.2 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 clinical staff to familiarize the Investigator (or designee) and clinical staff with the materials necessary for conducting the clinical study.

8.3 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.

8.4 Monitoring

The Sponsor will designate a Sponsor's 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.

8.5 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.

8.6 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.

8.7 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.

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

8.9 Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

INVESTIGATOR AGREEMENT

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

PPD

16 Aug 2018
ate

Principal Investigator
Covance Clinical Research Unit, Inc.

SPONSOR AGREEMENT

I have read the foregoing protocol and agree to the conduct of the study as described herein:

DocuSigned by:
PPD

17-Aug-18 | 04:51:48 EDT

Date

REFERENCES

1. LOXO-292 – Investigator's Brochure. (Version 3.0, 05 April 2018).

APPENDIX A - CLINICAL LABORATORY EVALUATIONS

Clinical Chemistry Panel (Fasted):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatinine
Glucose
Iron
Phosphorus
Potassium
Sodium
Thyroid-stimulating hormone (at Screening only)
Total bilirubin
Total protein
Triglycerides
Uric acid
Amylase
Lipase

Hematology:
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 (absolute and percent):
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

Drug Screen:
Including but not limited to the following:

Alcohol (ethanol, Day -1 only, by breathalyzer)
Amphetamines/methamphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine (metabolite)
Cotinine (by urinalysis)
Methadone
Opiates
Phencyclidine

Serology:
Hepatitis B surface antigen
Hepatitis B core antibody
Hepatitis C virus antibody
Human immunodeficiency virus antibody

APPENDIX B - BLOOD SAMPLING SUMMARY

Part 1			
Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Serology	4	1	4
Hematology	4	4	16
Clinical Chemistry	4	4	16
LOXO-292 and Total Radioactivity Sampling	6	25[a]	150
Metabolite Sampling	10	19[a]	190
Approximate Total Blood Volume			**376**
Part 2			
Serology	4	1	4
Hematology	4	4	16
Clinical Chemistry	4	4	16
LOXO-292, [^{14}C]-LOXO-292, and Total Radioactivity Sampling	6	25	150
Approximate Total Blood Volume			**186**

[a] Total number of blood samples collected in Part 1 for LOXO-292/total radioactivity analysis and for metabolite profiling/characterization is based on subject confinement until Day 22. If a subject meets the discharge criteria as defined in Table 6-1 earlier than Day 22, the total number of blood samples collected and the total blood volumes will be less.

APPENDIX C - ADVERSE EVENTS

1 ADVERSE EVENTS

1.1 Definition of Adverse Events

An adverse event (AE; or adverse experience) is defined as any untoward medical occurrence experienced by a patient or healthy subject, whether or not considered drug related by the Investigator (or designee). A treatment-emergent AE is an AE that is reported after a dose 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), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods, under placebo, or in a reference group receiving drug or nondrug therapy are also to be designated as AEs. All AEs, complaints, or symptoms that occur from the time informed consent is signed until the Safety Follow-up Call are to be recorded on the appropriate electronic Case Report Form (eCRF) (events that occur prior to consent are considered medical history). Documentation must be supported by an entry in the patient's source medical records. Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported in the eCRF as an AE. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product or other factors.

1.2 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**: Urgent intervention indicated
- **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.

The action taken with the investigational product in response to the AE should be provided at the time the event is reported. For this study, options for action taken include the following:

- **Dosing stopped**: Medication administration was stopped before or during dosing.

1.3 Pregnancy

As information is available, a pregnancy in a female partner of a male subject diagnosed during the study and for up to 6 months after study drug administration should be reported by the Investigator (or designee) via eFax to the Sponsor's Contact for Serious Adverse Event Reporting listed in the Study Identification section within 24 hours of being notified. The Sponsor's Contact for Serious Adverse Event Reporting will then forward the Pregnancy Form to the Investigator (or designee) for completion.

eFax: +1 (203) 643-2013

The 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 the Sponsor's Contact for Serious Adverse Event Reporting. At the completion of the pregnancy, the Investigator (or designee) will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a serious AE (SAE) (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator (or designee) should follow the procedures for reporting an SAE.

Male subjects will be instructed to notify the Investigator (or designee) immediately if they discover their sexual partner is pregnant. In this instance, the partner must provide written consent before pregnancy information can be collected. When a site becomes aware that the female partner of a male subject is pregnant, they are to contact the Covance Medical Monitor immediately (within 24 hours of the site staff becoming aware of the event) in addition to notifying the Sponsor's Contact for Serious Adverse Event Reporting via eFax.

1.4 Definition of Serious Adverse Events

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

- Death;
- A life-threatening adverse drug experience (ie, one that places the subject, in the view of the Investigator [or designee], at immediate risk of death; it does not mean an event that, had it occurred in a more severe form, might have caused 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.

1.5 Unexpected Adverse Drug Experience

An unexpected adverse drug experience is any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator's Brochure (IB) or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

1.6 Reporting

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected. Food and Drug Administration-reportable AEs will be reported by the Clinical Research Unit to the Sponsor, the Covance Medical Monitor, and the responsible Institutional Review Board (IRB).

Within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported, and within 24 hours of any SAE – either expedited or nonexpedited – being first recognized or reported, the Sponsor's Contact for Serious Adverse Event Reporting will be notified by the Investigator (or designee) in writing (eg, facsimile) using the following eFax number:

eFax: +1 (203) 643-2013

All SAEs occurring from the time of signing the Informed Consent Form through the Safety Follow-up Call must be reported. To report the SAE and/or potentially FDA-reportable AE, the completed SAE Report Form will be sent by eFax within 24 hours of first awareness. Incoming reports are reviewed during normal business hours. Additional reporting instructions and the SAE Report Form are provided in the Study Manual.

The Investigator (or designee) is not obligated to actively seek information regarding the occurrence of new SAEs beginning after the Safety Follow-up Call. However, if the Investigator (or designee) learns of such an SAE, and that event is deemed relevant to the use of study drug, he/she should promptly document and report the event. The Investigator (or designee) will be requested to supply detailed information as well as follow-up regarding the SAE.

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.