Statistical Analysis Plan 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

NCT05630287

Approval Date: 08-Oct-2018

STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Final
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Study Drug: LOXO-292

Sponsor Reference Number: LOXO- RET-18016
Covance Study Number: 8387024

Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical, pharmacokinetic (PK), and safety analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

PPD

Date

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Date

Sponsor approval:

PPD

Loxo Oncology, Inc.

Date

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3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	Analysis Data Model
AE	adverse event
A_{ef}	amount excreted in feces per sampling interval
A_{eu}	amount excreted in urine per sampling interval
AME	absorption, metabolism, and excretion
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
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
Blood/Plasma AUC Ratio	$AUC_{0-\infty}$ of total radioactivity in whole blood/$AUC_{0-\infty}$ of total radioactivity in plasma
BLQ	below the limit of quantitation
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
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
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Cum A_{ef}	cumulative amount excreted in feces
Cum A_{eu}	cumulative amount excreted in urine
Cum $\%f_e$	cumulative percentage of dose excreted in urine and feces
Cum $\%f_{ef}$	cumulative percentage of dose excreted in feces
Cum $\%f_{eu}$	cumulative percentage of dose excreted in urine
CV%	coefficient of variation

ECG	electrocardiogram
F	absolute bioavailability
$\%f_e$	percentage of dose excreted in urine and feces per sampling interval
$\%f_{ef}$	percentage of dose excreted in feces per sampling interval
$\%f_{eu}$	percentage of dose excreted in urine per sampling interval
ICF	Informed Consent Form
ICH	International Council for Harmonisation / International Conference on Harmonisation
IV	intravenous
λ_z	apparent terminal elimination rate constant
LLOQ	lower limit of quantification
log	logarithm (base e)
Max	maximum
MetID	metabolite profiling and identification
Min	minimum
N	number of subjects
n	number of observations
NC	not calculated
NR	no result
PK	pharmacokinetic(s)
Plasma LOXO-292/ Total Radioactivity AUC Ratio	$AUC_{0-\infty}$ of LOXO-292 in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma
QTc	QT correction; QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
R^2	adjusted coefficient for determination of exponential fit
RET	rearranged during transfection
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
$t_{½}$	apparent terminal elimination half-life

TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time to maximum observed concentration
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

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version dated 15 June 2018, Protocol Amendment 1 dated 12 July 2018, and Protocol Amendment 2 dated 15 August 2018).

This SAP describes the planned analysis of the safety, tolerability, and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of safety and PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Loxo Oncology, Inc. and Covance Early Clinical Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Loxo Oncology, Inc. and Covance Early Clinical Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Council for Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

5.1 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 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.

The secondary objective of Part 1 of this study is:

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

5.2 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.

6 STUDY DESIGN

This study is 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, to evaluate the fecal recovery of total radioactivity following IV dosing 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 receives a dose of LOXO-292 per part per Protocol and completes sufficient LOXO-292 plasma and urine sampling, total radioactivity sampling, [^{14}C]-LOXO-292 plasma and urine sampling (Part 2 only), 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 6-1 and a schematic of the study design of Part 2 is presented in Figure 6-1.

Figure 6-1 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 6-2 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.

6.1 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 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, 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).

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.

6.2 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, 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).

7 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Part 1:		
Study Treatment Name	**Abbreviation**	**Treatment order on TFL**
single oral dose solution of 160 mg of [^{14}C]-LOXO-292	160 mg [^{14}C]-LOXO-292	1
Part 2:		
2×80-mg capsules LOXO-292 + IV dose of < 100 µg of [^{14}C]-LOXO-292	160 mg oral dose LOXO-292 + < 100 µg IV dose [^{14}C]-LOXO-292	1

8 SAMPLE SIZE JUSTIFICATION

CCI

9 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Populations** for Parts 1 and 2 will consist of all subjects who received at least 1 dose of study treatment and have at least 1 post-dose safety assessment.

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

Data for each subject will be included in the summary statistics and statistical comparisons of PK parameters with the exceptions described as follows:

- Data from subjects who experience emesis at or before 2 times median T_{max} for the given treatment may be excluded from the summary statistics and data presentation of PK parameters for the given treatment.
- Data from subjects who significantly violate protocol inclusion or exclusion criteria, deviate significantly from the protocol, or have unavailable or incomplete data which may influence the PK analysis will be excluded from the PK Population.

Any subject or data excluded from the analysis will be identified, along with their reason for exclusion, in the CSR.

The **All Subjects Populations** for Parts 1 and 2 will consist of any subjects who enrolled on to the study (signed informed consent, met all inclusion and exclusion criteria, and had study assessments recorded on the database as per the protocol).

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Populations for Parts 1 and 2. Summary statistics will be performed for subjects included in the relevant analysis populations (Safety/PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum (Min), maximum (Max), number of subjects (N), and number of observations (n). For log-normal data (e.g., the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics and data presentation, unrounded data will be used.

Missing values will not be imputed, with the exception of missing PK predose concentrations, which may be set to zero for PK analysis, with Sponsor approval (see Section 0).

Data analysis will be performed using SAS® Version 9.4 or higher.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

10.1.1 Definition of Baseline and Change from Baseline

If changes from baselines are calculated, baseline for each parameter is defined as the last value measured prior to the first dose, including repeat (vital signs and electrocardiograms [ECGs]) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings).

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading.

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. All results not taken at a scheduled timepoint for other data types (e.g., clinical laboratory parameters) are unscheduled. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries with the exception that they may be used as baseline.

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarized for each part and listed. Subject disposition will be summarized for each part and listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Pharmacokinetic parameters will be determined from plasma concentrations of LOXO-292 and [^{14}C]-LOXO-292 and whole blood and plasma concentrations of total radioactivity using a

model-independent approach performed using Phoenix WinNonlin (Certara USA, Inc.) version 6.4 or higher. Pharmacokinetic parameters for relevant metabolites of LOXO-292 may be calculated in Part 1 by the Radioanalysis Department or Metabolite Profiling Lab and reported in those phase sub-reports, as deemed appropriate. In Parts 1 and 2, additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded on the eCRF. If actual times are missing, nominal times may be used with Sponsor approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

Part 1

The following PK parameters will be determined for each subject, where possible, from the plasma concentrations of LOXO-292 and whole blood and plasma concentrations of total radioactivity:

Parameter	Definition
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 and 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
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity
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 elimination 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.

The AUC ratios (AUC total radioactivity in whole blood to AUC total radioactivity in plasma, and AUC of Plasma LOXO-292 to AUC of plasma total radioactivity) will be based on $AUC_{0-\infty}$. Where $AUC_{0-\infty}$ cannot be reliably calculated, an alternative AUC measure, such as AUC_{last} or AUC to a common timepoint, may be used.

Additionally, blood-to-plasma concentration ratios at each sampling timepoint will be calculated (by the Covance Radioanalysis Department) and reported in the radioanalysis report 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:

Parameter	Definition
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:

Parameter	Definition
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

All PK parameters for total radioactivity in urine and feces will be calculated by the Covance Radioanalysis Department and will be reported in the radioanalysis report. The Covance Radioanalysis Department will also calculate and report the amount of total radioactivity in total excreta (feces + urine).

The amount excreted in urine or feces (A_{eu} or A_{ef}) for each collection interval will be calculated as the product of concentration and sample weight; Cum A_{eu} and Cum A_{ef} will be calculated by summing the A_{eu} or A_{ef} values for each collection interval.

The percentage of the dose excreted in urine or feces ($\%f_{eu}$ or $\%f_{ef}$) will be calculated for each collection interval (i) and cumulatively according to the following formula:

$$\%f_e(i) = \frac{A_e(i)}{dose} \times 100$$

Part 2

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

Parameter	Definition
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 as described for Part 1
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated as described for Part 1
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity
λ_z	Apparent terminal elimination rate constant
$t_{1/2}$	Apparent terminal elimination half-life (whenever possible), calculated as described for Part 1
F	Absolute bioavailability, calculated as $F = \frac{AUC_{0-\infty}\text{ (oral)} \times \text{Dose (IV)}}{AUC_{0-\infty}\text{ (IV)} \times \text{Dose (oral)}}$
CL/F	Apparent systemic clearance
V_z/F	Apparent volume of distribution during the terminal elimination phase

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

Parameter	Definition
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 as described for Part 1

$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated as described for Part 1
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity
λ_z	Apparent terminal elimination rate constant
$t_{1/2}$	Apparent terminal elimination half-life (whenever possible), calculated as described for Part 1
CL	Systemic clearance
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution during the terminal phase

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:

Parameter	Definition
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 = Cum $A_{eu}/AUC_{0-\infty}$ or AUC over a common timepoint between urine and plasma sample $AUC_{0-\infty}$ may be used, if appropriate
$\%f_{eu}$	cumulative percentage of dose excreted in urine
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:

Parameter	Definition
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

The following excretion parameters will be calculated, whenever possible, based on total radioactivity in total (urine+feces) excreta:

Parameter	Definition
$\%f_e$	percentage of dose excreted in urine and feces per sampling interval, where $\%f_e = \%f_{eu} + \%f_{ef}$
Cum $\%f_e$	cumulative percentage of dose excreted in urine and feces, calculated as the sum of the percentage of dose excreted in urine and feces for each collection period

C_{max} and T_{max} will be obtained directly from the plasma and whole blood concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported.

The amount excreted (A_e) in urine and feces for each collection interval will be calculated as the product of analyte concentration in urine or feces and sample weight. Cumulative A_e will be calculated by summing the A_e values for each collection interval over the sampling period.

10.3.2 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows;

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose concentration is missing, these values may be set to zero with Sponsor approval

10.3.3 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

10.3.3.1 Number of Data Points

At least 3 data points will be included in the regression analysis and preferably should not include C_{max}.

10.3.3.2 Goodness of Fit

When assessing terminal elimination phases, the R^2 adjusted value will be used as a measure of the goodness of fit of the data points to the determined line.

Regression-based parameters ($AUC_{0-\infty}$, $\%AUC_{extrap}$, λ_z, $t_{1/2}$, CL/F, CL, V_z/F, V_z, and V_{ss}) will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

10.3.3.3 Period of Estimation

The time period used for the estimation of apparent terminal elimination half-lives will be over at least 2 half-lives, where possible.

Where an elimination half-life is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the study report.

10.3.4 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma or whole blood concentrations above the lower limit of quantification (LLOQ).
- For any partial AUC determination, nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the pharmacokineticist.
- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is between 20 to 30% will be reported, flagged, and included in the descriptive statistics, whilst $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be reported and flagged, but excluded from descriptive statistics.

10.3.5 Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

Positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and data presentation at the discretion of the pharmacokineticist.

10.4 Presentation of Pharmacokinetic Data

10.4.1 Presentation of Pharmacokinetic Concentration Data

Plasma and Whole Blood

The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are less than three values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

Urine and Feces

Part 1 urine and feces concentration data will be reported in a separate radioanalysis report.

Part 2 urine and feces concentration data will be listed only.

10.4.2 Presentation of Pharmacokinetic Parameters

For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

10.4.3 Pharmacokinetic Statistical Methodology

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.

10.5 Safety and Tolerability Assessments

10.5.1 Adverse Events

All AEs occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 21.0. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose. The AE severity and relationship are determined by the investigator at the site. The severity grade of each AE will be based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) 5-point severity scale (Grade 1, 2, 3, 4 and 5). Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, part, severity grade, relationship to study treatment, outcome, and action; however, only treatment-emergent AEs (TEAEs) will be summarized. The frequency of TEAEs (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) will be summarized by part, treatment, and by system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study treatment (those that have a relationship of related). Any life-threatening or serious AEs will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

For orally administered LOXO-292 and [^{14}C]-LOXO-292, onset times postdose are calculated from the time of dose administration (Parts 1 and 2).

For [^{14}C]-LOXO-292 administered as an IV push, onset times postdose are calculated from the start of infusion (Part 2 only).

10.5.2 Clinical Laboratory Parameters

Clinical chemistry and hematology will be summarized by part. In addition, all clinical chemistry, hematology, and urinalysis data outside the clinical reference ranges will be listed by parameter for each part.

Values for any clinical chemistry, hematology, and urinalysis values outside the clinical reference ranges will be flagged on the individual subject data listings.

All clinically significant laboratory evaluation data (including clinical chemistry, hematology, and urinalysis) will be listed by parameter for each part.

10.5.3 Vital Signs

Vital signs data (including oral temperature, supine blood pressure, heart rate, and respiratory rate) will be listed and summarized by part, together with changes from baseline.

Figures of mean vital signs and mean changes from baseline profiles will be presented by part.

Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings.

10.5.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval corrected for heart rate using Fridericia's method (QTcF), the PR, and QT intervals, the QRS duration, and heart rate.

The ECG data will be listed and summarized by part. ECG interpretation will be listed by subject and part.

Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listings.

An outlier analysis will be performed including all maximum individual postdose measurements (not the mean data), including all repeat and unscheduled readings. All incidences of maximum QTc and QTcF (>450 and ≤ 480, >480 and ≤ 500, and >500 ms) and all incidences of maximum change from baseline in QTc and QTcF (>30 and ≤ 60 and >60 ms) will be flagged on the listing.

10.5.5 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analysed.

10.5.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.