Statistical Analysis Plan: LOXO-BTK-20007 (Final version 1.0)

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

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# Statistical Analysis Plan

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

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## LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [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 |
| $AUC_{0\text{-}inf}$ | area under the concentration-time curve from time 0 extrapolated to infinity |
| $AUC_{0\text{-}t}$ | area under the concentration-time curve from time 0 to the last quantifiable concentration |
| BLQ | below the limit of quantification |
| CDISC | Clinical Data Interchange Standards Consortium |
| CK | creatine kinase |
| CL | total clearance |
| CL/F | apparent total 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 |
| ECG | electrocardiogram |
| EOS | end of study |
| EOT | end of treatment |
| ET | early termination |
| 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 |
| Geom Mean | geometric mean |
| HYDF? | How Do You Feel? |
| $\lambda z$ | apparent terminal elimination rate constant |
| LLOQ | lower limit of quantification |
| ln | natural log |
| LSM | Least squares mean |
| ICF | informed consent form |

| | |
|---|---|
| ICH | International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IV | intravenous |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MetID | metabolite profiling and identification |
| NC | not calculated |
| NR | no result |
| PK | pharmacokinetic(s) |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| TEAE | treatment-emergent adverse event |
| TFL | table, figure, and listing |
| $t_{1/2}$ | terminal elimination half-life |
| $t_{max}$ | time to maximum observed concentration |
| UA | urinalysis |
| $V_{ss}$ | volume of distribution at steady state |
| $V_z$ | volume of distribution |
| $V_z/F$ | apparent volume of distribution |
| WHODrug | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 29 June 2020) and electronic case report form.

This SAP describes the planned analysis of the pharmacokinetic (PK), and safety and tolerability 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 shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Loxo Oncology, Inc. A limited amount of information about this study (eg, 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 approved, they will serve as the template for this study's CSR.

This SAP supersedes any 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 accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Loxo Oncology, Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

# 2. STUDY OBJECTIVES

## 2.1. Primary Objectives

Part 1:

The primary objectives of Part 1 of the study are:

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

Part 2:

The primary objectives of Part 2 of the study are:

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

### 2.2. Secondary Objectives

Part 1:

The secondary objective of Part 1 of the study is:

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

Part 2:

The secondary objective of Part 2 of the study is:

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

## 3. STUDY ENDPOINTS

### 3.1. Primary Endpoints

Part 1:

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

- area under the concentration-time curve (AUC) from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$)
- AUC from time zero to the last quantifiable concentration ($AUC_{0\text{-}t}$)
- maximum observed concentration ($C_{max}$)

- time to maximum concentration ($t_{max}$)
- apparent terminal elimination half-life ($t_{1/2}$)
- apparent systemic clearance (LOXO-305 only; CL/F)
- apparent volume of distribution (LOXO-305 only; $V_z/F$)
- $AUC_{0\text{-}inf}$ of plasma LOXO-305 relative to $AUC_{0\text{-}inf}$ of plasma total radioactivity ($AUC_{0\text{-}inf}$ Plasma LOXO-305/Total Radioactivity Ratio)
- $AUC_{0\text{-}inf}$ of whole blood total radioactivity to $AUC_{0\text{-}inf}$ of plasma total radioactivity ($AUC_{0\text{-}inf}$ Blood/Plasma Ratio).

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

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

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

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

The primary outcome for metabolites will be derived:

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

Part 2:

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

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

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

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

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

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

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

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

Other PK parameters may also be reported.

### 3.2. Secondary Endpoints

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

- monitoring adverse events (AEs)
- clinical laboratory evaluations
- 12-lead electrocardiogram (ECG) parameters
- vital signs measurements
- Concomitant medication
- physical examinations.

## 4. STUDY DESIGN

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

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

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

Part 2 is designed to determine the absolute bioavailability of LOXO-305, to evaluate the plasma concentration of LOXO-305 and plasma PK of [$^{14}$C]-LOXO-305 and total radio activity, and to evaluate the urinary excretion of [$^{14}$C]-LOXO-305 and total radioactivity, to evaluate the fecal excretion of [$^{14}$C]-LOXO-305 and total radioactivity, and to assess the safety and tolerability of LOXO-305 and [$^{14}$C]-LOXO-305. Subjects in Part 2 will be administered a single oral dose of 200 mg of LOXO-305 as 2 × 100-mg tablets followed 2 hours later by a single dose of < 100 µg of [$^{14}$C]-LOXO-305 (containing ~1 µCi of radioactivity [microtracer]) administered as an IV push over approximately 2 minutes.

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

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

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

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

**Figure 1 Study Design Schematic: Part 1**

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

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

**Figure 2 Study Design Schematic: Part 2**

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

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

Part 1:

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

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

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

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

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

Part 2:

After a Screening period of up to 28 days, subjects will check in to the CRU on Day -1 to confirm eligibility and to become familiar with study procedures. On the morning of Day 1,

following an overnight fast of at least 10 hours, subjects will receive a single oral dose of 200 mg of LOXO-305 as 2 × 100-mg tablets and followed 2 hours later by a single dose of < 100 µg of [$^{14}$C]-LOXO-305 (containing ~1 µCi of radioactivity [microtracer]) administered as an IV push over approximately 2 minutes. Subjects will be confined at the CRU from the time of Check-in (Day -1) until Day 9 and will be discharged from the CRU after completing all discharge procedures. Subjects will receive a Follow-up Call approximately 7 days after Clinic Discharge.

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

Part 1 and Part 2:

In this study, physical examinations, 12-lead ECGs, vital sign measurements, How Do You Feel? (HDYF?) inquiries, clinical chemistry panel, coagulation parameters, hematology panel, urinalysis (UA), and recording of concomitant medications will be performed at specified times during the study. AEs and serious adverse events (SAEs) will be collected beginning at informed consent. AEs will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until Early Termination [ET] if the subject discontinues from the study and does not complete a Follow-up Phone Call), either as subject medical history (if the event is reported as beginning prior to signing of the ICF or if the event occurs prior to study drug administration on Day 1 and is assessed as not related to study procedures by the Investigator [or designee]) or as AEs (if the event occurs after signing of the ICF but prior to study drug administration on Day 1 and is assessed as related to study procedures by the Investigator [or designee], or if the event occurs after study drug administration on Day 1 through End of Treatment [EOT] or ET regardless of relationship to study drug). From EOT or ET through EOS, only AEs assessed as related to study drug by the Investigator (or designee) are to be reported. All SAEs that develop from the time of ICF signing until EOS (or ET, if the subject discontinues from the study and does not complete a Follow-up Phone Call) are to be reported. Study completion is defined as the time of the last subject's Follow-up Phone Call.

## 5. SAMPLE SIZE JUSTIFICATION

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

## 6. STUDY TREATMENTS

In Part 1, the study treatment name to be used in the TFLs is 200 mg [$^{14}$C]-LOXO-305 oral solution.

In Part 2, the study treatment name is 2x100mg LOXO-305 Tablets + < 100 µg [14C] LOXO-305 IV Solution.

## 7. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those related to COVID-19, will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

### 7.1. All Subjects Population

The all subjects population will include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

### 7.2. Safety Population

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

### 7.3. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of [$^{14}$C]-LOXO-305 or LOXO-305 and have at least 1 quantifiable PK concentration, and for whom at least 1 PK parameter can be computed. A subject may be excluded from the PK summary statistics if the subject has an AE of vomiting that occurs at or before 2 times the median $t_{max}$.

## 8. STATISTICAL METHODOLOGY

### 8.1. General Considerations

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they completed all protocol-specified procedures and assessments for the EOT visit. Any subject who discontinued the study will be identified accordingly in the listings. Summaries will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

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

Where reference is made to ‘all calculations’, this includes, but is not limited to, summary statistics, baseline derivation, and changes from baseline.

### 8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As ET data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.
- Post dose repeats and unscheduled assessments will not be included in calculation of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.
- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 8.6.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

All protocol deviations and data issues (eg missing data, out of protocol window) that occur during the study, including those related to COVID-19, will be considered prior to database lock for their severity/impact on how the data will be displayed.

### 8.1.2. Repeat and Unscheduled Assessments

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original scheduled value will be used in all calculations post dose. In the event of any repeats or unscheduled measurements taken pre-dose the values will be considered when determining the baseline value for each period.

Post dose repeats, unscheduled assessments, and ET measurements will be excluded from all calculations, with the exception of the baseline derivation (see Section 8.1.3).

### 8.1.3. Definitions of Baseline and Change from Baseline

Baseline value is defined as the last non missing measurement before administration of LOXO-305 in each part of the study.

In general, baseline for Part 1 and Part 2 refers to the pre-dose value collected on Day 1. For laboratory tests, baseline is the value collected on Day -1.

If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing of LOXO-305 in each part of the study.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The mean change from baseline will be defined as the mean of the individual changes from baseline for all subjects.

See Section 8.1.2 for more detail on handling repeat and unscheduled readings in the calculations.

## 8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by part will be provided, based on the all subjects population.

## 8.3. Demographics and Baseline Characteristics

The demographics and baseline characteristics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by part will be provided, based on the safety population.

## 8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to the first dose of LOXO-305. Concomitant medication will be defined as medication that starts during or after the first dose or starts but does not end prior to the first dose.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2020. Prior and concomitant medications will be listed.

## 8.5. Pharmacokinetic Assessments

### 8.5.1. Pharmacokinetic Analysis

Part 1 PK parameters will be determined where possible from plasma concentrations of LOXO-305 and whole blood and plasma concentrations of total radioactivity. Part 2 PK parameters will be determined from plasma concentrations of LOXO-305, plasma, urine, and feces concentrations of [$^{14}$C]-LOXO-305, and plasma concentrations of total radioactivity,

urine and feces concentrations of total radioactivity. Parameters will be determined using a model-independent approach performed using Phoenix WinNonlin (Certara USA, Inc.) version 8.1 or higher. Additional PK parameters beyond those listed in subsections below may be determined where appropriate.

PK analysis will be carried out using the actual dose administered (mg for oral doses and µg for IV dose) and actual blood sampling times postdose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time. Calculation of PK parameters for urine and feces will be determined using nominal collection intervals.

In both parts, the whole blood and plasma parameters $C_{max}$, $t_{last}$, and $t_{max}$ will be obtained directly from the concentration-time profiles. If $C_{max}$ occurs at more than 1 timepoint, $t_{max}$ will be assigned to the first occurrence of $C_{max}$.

#### 8.5.1.1. Part 1 - Mass Balance

Concentration ratios of whole blood total radioactivity to plasma total radioactivity, individual and cumulative mass balance of total radioactivity (amount (Ae) and percentage of dose (%fe) recovered as total radioactivity in urine, feces, emesis (if applicable) and total excreta in all excreta) will be calculated where possible by Covance radioanalysis laboratory and will be reported separately in the radioanalysis report.

The following PK parameters will be determined for each subject, where possible, from the plasma concentrations of LOXO-305 and whole blood and plasma concentrations of total radioactivity:

| Parameter | Units[a] | Definition |
|---|---|---|
| $AUC_{0-t}$ | h*ng/mL[b] | area under the concentration-time curve from hour 0 to the time of the last quantifiable concentration ($t_{last}$)[c] |
| $AUC_{0-inf}$ | h*ng/mL[b] | area under the concentration-time curve from time 0 extrapolated to infinity[d] |
| $\%AUC_{extrap}$ | % | percentage of $AUC_{0-inf}$ due to extrapolation from the last quantifiable concentration to infinity |
| $C_{max}$ | ng/mL[b] | maximum observed concentration |
| $t_{max}$ | h | time of the maximum observed concentration |
| $t_{last}$ | h | time of the last quantifiable concentration |
| $t_{1/2}$ | h | apparent terminal elimination half-life |
| CL/F | L/h | apparent systemic clearance (LOXO-305 only) |
| $V_z/F$ | L | apparent volume of distribution during the terminal phase (LOXO-305 only) |
| $AUC_{0-inf}$ Plasma LOXO-305/Total Radioactivity Ratio | | $AUC_{0-inf}$ of plasma LOXO-305 relative to $AUC_{0-\infty}$ of plasma total radioactivity |

| | |
|---|---|
| $AUC_{0\text{-}inf}$ Blood/Plasma Total Radioactivity Ratio | $AUC_{0\text{-}inf}$ of whole blood total radioactivity to $AUC_{0\text{-}\infty}$ of plasma total radioactivity |

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] For total radioactivity, $C_{max}$ and AUC units will be presented as mass equivalents (ng Eq/g and h*ng Eq/g, respectively).
[c] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing and decreasing concentrations.
[d] Based on the last observed quantifiable concentration

### 8.5.1.2. Part 2 - Absolute Bioavailability

**Oral Dose Plasma PK**

The following PK parameters will be calculated for each subject, where possible, based on the plasma concentrations of LOXO-305:

| Parameter | Units[a] | Definition |
|---|---|---|
| $AUC_{0\text{-}t}$ | h*ng/mL | area under the concentration-time curve from hour 0 to the time of the last quantifiable concentration ($t_{last}$)[b] |
| $AUC_{0\text{-}inf}$ | h*ng/mL | area under the concentration-time curve from hour 0 extrapolated to infinity[c] |
| $\%AUC_{extrap}$ | % | percentage of AUC due to extrapolation from the last quantifiable concentration to infinity |
| $C_{max}$ | ng/mL | maximum observed concentration |
| $t_{max}$ | h | time of the maximum observed concentration |
| $t_{last}$ | h | time of the last quantifiable concentration |
| $t_{1/2}$ | h | apparent terminal elimination half-life |
| CL/F | L/h | apparent systemic clearance |
| $V_z/F$ | L | apparent volume of distribution during the terminal phase |
| F | | absolute bioavailability; expressed as a ratio, calculated as $F = \frac{AUC_{0\text{-}inf}(oral) \times Dose(IV)}{AUC_{0\text{-}inf}(IV) \times Dose(oral)}$ |

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing and decreasing concentrations.
[c] Based on the last observed quantifiable concentration

**IV Dose Plasma PK**

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

| Parameter | Units[a] | Definition |
|---|---|---|
| $AUC_{0\text{-}t}$ | h*pg/mL | area under the concentration-time curve from hour 0 to the time of the last quantifiable concentration ($t_{last}$)[b] |
| $AUC_{0\text{-}inf}$ | h*pg/mL | area under the concentration-time curve from hour 0 extrapolated to infinity[c] |

| | | |
|---|---|---|
| $\%AUC_{extrap}$ | % | percentage of AUC due to extrapolation from the last quantifiable concentration to infinity |
| $C_{max}$ | pg/mL | maximum observed concentration |
| $t_{max}$ | h | time of the maximum observed concentration |
| $t_{last}$ | h | time of the last quantifiable concentration |
| $t_{1/2}$ | h | terminal elimination half-life |
| CL | L/h | total clearance ([$^{14}$C]-LOXO-305 only) |
| $V_z$ | L | volume of distribution during the terminal phase ([$^{14}$C]-LOXO-305 only) |
| $V_{ss}$ | L | volume of distribution at steady state ([$^{14}$C]-LOXO-305 only) |

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing and decreasing concentrations.
[c] Based on the last observed quantifiable concentration

### 8.5.1.3. Part 2 - IV Dose Excretion PK

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

| Parameter | Units | Definition |
|---|---|---|
| $A_{eu}$ | µg[a] | amount excreted in urine per sampling interval |
| Cum $A_{eu}$ | µg[a] | cumulative amount excreted in urine |
| $CL_R$ | L/h | renal clearance ([$^{14}$C]-LOXO-305 only) |
| $f_{eu}$ | % | 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 |

[a] For total radioactivity, units will be presented as mass equivalents (µg Eq).

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

| Parameter | Units | Definition |
|---|---|---|
| $A_{ef}$ | µg[a] | amount excreted in feces per sampling interval |
| Cum $A_{ef}$ | µg[a] | 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 |

[a] For total radioactivity, units will be presented as mass equivalents (µg Eq).

In addition, the following excretion parameters will be calculated, where possible, based on total radioactivity in total (urine+feces) excreta:

| Parameter | Units | 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 $f_e$ in urine + feces |

### 8.5.1.4. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant ($\lambda_z$) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including $C_{max}$, and the adjusted coefficient for determination of exponential fit ($R^2$-adj) of the regression line is ≥0.7. Parameters requiring $\lambda_z$ for their calculation (eg, $AUC_{0\text{-inf}}$, $t_{1/2}$, CL/F, CL, $V_z$/F, $V_z$, and $V_{ss}$) will only be calculated if the $R^2$-adj value of the regression line is ≥0.7.

The following regression-related diagnostic PK parameters will be determined, when possible:

| Parameter | Units | Definition |
|---|---|---|
| $\lambda_z$ | 1/h | apparent terminal elimination rate constant |
| $\lambda_z$ Upper | h | end of exponential fit |
| $\lambda_z$ Lower | h | start of exponential fit |
| $\lambda_z$ N | NA | number of data points included in the log-linear regression |
| $\lambda_z$ Span Ratio | NA | time period over which $\lambda_z$ was determined as a ratio of $t_{1/2}$ |
| $R^2$-adj | NA | adjusted coefficient for determination of exponential fit |

NA not applicable

Where possible, the span of time used in the determination of $\lambda_z$ (ie, the difference between $\lambda_z$ Upper and $\lambda_z$ Lower) should be ≥2 half-lives. If the $\lambda_z$ Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

### 8.5.1.5. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow $C_{max}$.

For any partial AUC determination (eg, $AUC_{0\text{-}24}$), 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.

If the extrapolated area is >30%, $AUC_{0\text{-inf}}$ (and derived parameters) will be excluded from the summary statistics.

If $AUC_{0\text{-}inf}$ cannot be determined reliably for all subjects and/or treatments, an alternative AUC measure, such as AUC to a fixed timepoint or $AUC_{0\text{-}t}$ may be used in calculation of ratios or absolute bioavailability.

### 8.5.1.6. Calculation of Excretion Parameters (Part 2)

The amount of the dose administered recovered over each time interval t1 to t2 ($A_{e1\text{-}t2}$) in urine or feces for [$^{14}$C]-LOXO-305 and total radioactivity will be calculated as the product of urine analyte concentration and urine sample volume or feces analyte concentration and fecal sample weight. Where only urine sample weight is supplied, a specific gravity of 1 g/mL will be assumed, and it will be considered equivalent to urine volume. Cumulative $A_{eu}$ or $A_{ef}$ will be calculated by summing the respective matrix $Ae_{t1\text{-}t2}$ values across collection intervals.

The percentage of the dose administered recovered ($f_e$) over each time interval t1 to t2 ($f_{et1\text{-}t2}$) in urine or feces as [$^{14}$C]-LOXO-305 and total radioactivity will be calculated for each sample collection interval as follows:

$f_{et1\text{-}t2} = (A_{et1\text{-}t2} / \text{dose}) \times 100$

Cumulative $f_{eu}$ or $f_{ef}$ will be calculated by summing the respective matrix $f_{et1\text{-}t2}$ and combined matrix $f_{et1\text{-}t2}$ (urine + feces) values in the same manner as $A_{eu}$ and $A_{ef}$.

Renal clearance ($CL_R$) will be calculated over 0-t2 according to the following formula, where cumulative $A_{eu}$ and plasma AUC are calculable to the same end time (t2):

$CL_R = A_{eu0\text{-}t2} / AUC_{0\text{-}t2}$

Alternatively, $AUC_{0\text{-}inf}$ may be used if urinary excretion of the dose is considered to be complete and $AUC_{0\text{-}inf}$ is well characterized.

### 8.5.1.7. Criteria for Handling Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma and whole blood concentrations BLQ will be assigned a value of 0 before the first measurable concentration and thereafter BLQs will be treated as missing. The following rules apply with special situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma or whole blood concentration is missing, it will be set to zero by default within Phoenix WinNonlin.

Urine or feces concentrations that are BLQ will be set to zero for the calculation of $A_{eut1\text{-}t2}$ and $A_{eft1\text{-}t2}$, respectively.

#### 8.5.1.8. Treatment of Outliers in Pharmacokinetic Analysis

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

Any quantifiable predose concentration value will be considered anomalous and set to missing for the PK analysis.

### 8.5.2. Presentation of Pharmacokinetic Data

Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For PK concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and CV% of geometric mean will be reported as not calculated (NC).
- If there are fewer l than 3 values in the data series, only the minimum, maximum and N will be presented. The other summary statistics will be denoted as not calculated (NC).

For PK parameters the following rule will apply:

- Geometric mean and coefficient of variation will not be calculated for $t_{last}$ or $t_{max}$.

PK analysis will use actual times as recorded on the electronic case report form.

### 8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables by part, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by time postdose will be provided for plasma and whole blood PK concentrations. All figures will be produced on both linear and semi-logarithmic scales. The +SD bars will only be displayed on the linear scale.

Summary tables by part will be provided for all PK parameters, with the exception of diagnostic regression-related PK parameters. Summary statistics (n, Mean, SD, CV%, minimum, median, maximum, geometric mean [Geom Mean] and geometric CV% [Geom CV%]) will be calculated for plasma LOXO-305 PK parameters. Excluded subjects will be listed in the PK parameter tables, but will be excluded from the summary statistics and noted as such in the tables.

Separate summary tables by time interval will be provided for excretion parameters and cumulative excretion parameters.

No inferential statistical analyses are planned.

### 8.6. Safety and Tolerability Assessments

#### 8.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. All AEs will be assigned severity grade using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after the first dose, or starts prior to the first dose and increases in severity after the first dose.

A treatment-related TEAE will be defined as a TEAE with a relationship of related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized by part for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by part
- TEAEs by severity and part
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by part
- Treatment-related TEAEs by severity and part

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class and preferred term
- Preferred term and treatment/part
- System organ class, preferred term, day of onset, and treatment/part

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to dosing.
- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.

- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If the severity of a TEAE is missing, a TEAE will be counted under the maximum severity possible, up to Grade 4 in the absence of a fatal outcome.

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

### 8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, with changes from baseline, will be listed; any value outside the clinical reference range will be flagged, and whether the out of range value was deemed clinically significant or not clinically significant will be indicated. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

The observed results and change from baseline for clinical chemistry, hematology, and coagulation parameters will be summarized descriptively by study part and timepoint.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, <x and ≤x values will be set to 0 whereas >x and ≥x values will be set to x.

### 8.6.3. Vital Signs Parameters

All vital signs parameters with changes from baseline will be listed; any value outside the clinical reference range will be flagged, and whether the out of range value was deemed clinically significant or not clinically significant will be indicated

The observed results and change from baseline for all vital signs parameters will be summarized descriptively by part and timepoint.

### 8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters with changes from baseline will be listed; any value outside the clinical reference range will be flagged, and whether the out of range value was deemed clinically significant or not clinically significant will be indicated.

The observed results and change from baseline for all 12-lead ECG parameters will be summarized descriptively by part and timepoint. QTcF values that are > 450 msec and increase from baseline > 30 msec will be flagged in the data listing.

### 8.6.5. Other Assessments

Medical history and physical examination will be listed. Any physical examination abnormalities reported will also be flagged as clinically significant or not clinically significant as indicated.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

### 8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

## 9. INTERIM ANALYSES

No interim analyses are planned.

## 10. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There was a minor change from the protocol-specified analyses in Protocol Version 1.0 dated 29 June 2020. Section 2.2.1 Primary Endpoints stated in Part 2 that “The primary PK endpoints of LOXO-305 and total radioactivity in plasma following oral administration of LOXO-305 are as follows”, however total radioactivity in plasma will be calculated after the IV dose.

## 11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

2. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

## 12. APPENDICES

### Appendix 1: Document History

| Status, Version | Date of Change | Summary/Reason for Changes |
|---|---|---|
| Final, Version 1.0 | NA | NA; the first version. |

NA = not applicable