Statistical Analysis Plan LOXO-BTK-20010

A Phase I, Open-label, Fixed-sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on CYP1A2, CYP2C9, and CYP2Cl9 Substrates Using a Probe Drug Cocktail in Healthy Subjects

NCT06215430

Approval date: 26-Mar-2021

Statistical Analysis Plan

A Phase I, Open-label, Fixed-sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on CYP1A2, CYP2C9, and CYP2C19 Substrates using a Probe Drug Cocktail in Healthy Subjects

SAP Status: Sponsor Final
SAP Version: 1.0
SAP Date: 26MAR2021

Investigational Product: LOXO-305

Protocol Reference: LOXO-BTK-20010
Covance Study: 8419689

Sponsor:
Loxo Oncology, Inc.
A wholly owned subsidiary of Eli Lilly and Company
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080
USA

Coordinating Investigator Study Site:
Covance Clinical Research Unit Inc.
1341 West Mockingbird Lane, Suite 200E
Dallas, Texas 75247
USA

Coordinating Principal Investigator:
PPD

TABLE OF CONTENTS

TITLE PAGE 1
TABLE OF CONTENTS 2
LIST OF ABBREVIATIONS 4
1. INTRODUCTION 6
2. STUDY OBJECTIVES 6
2.1. Primary Objective 6
2.2. Secondary Objective 6
3. STUDY ENDPOINTS 6
3.1. Primary Endpoints 6
3.2. Secondary Endpoints 7
4. STUDY DESIGN 7
5. SAMPLE SIZE JUSTIFICATION 9
6. STUDY TREATMENTS 9
7. DEFINITIONS OF POPULATIONS 10
7.1. All Subjects Population 10
7.2. Safety Population 11
7.3. Pharmacokinetic Population 11
8. STATISTICAL METHODOLOGY 11
8.1. General 11
8.1.1. Calculation of the Summary Statistics 11
8.1.2. Repeat and Unscheduled Readings 12
8.1.3. Definitions of Baseline and Change from Baseline 12
8.2. Subject Disposition and Population Assignment 13
8.3. Screening Demographics and Baseline Characteristics 13
8.4. Prior and Concomitant Medication 13
8.5. Pharmacokinetic Assessments 13
8.5.1. Pharmacokinetic Analysis 13
8.5.2. Presentation of Pharmacokinetic Data 16
8.5.3. Pharmacokinetic Statistical Methodology 16
8.6. Safety and Tolerability Assessments 17
8.6.1. Adverse Events 17
8.6.2. Clinical Laboratory Parameters 19

8.6.3. Vital Signs Parameters 19
8.6.4. 12-lead Electrocardiogram Parameters 19
8.6.5. Other Assessments 20
8.6.6. Safety and Tolerability Statistical Methodology 20
9. INTERIM ANALYSES 20
10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES 20
11. REFERENCES 20
12. APPENDICES 21

LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

$\%AUC_{extrap}$	percentage extrapolation for AUC_{0-inf}
AUC_{0-24}	area under the concentration-time curve from hour 0 to 24 hours postdose
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
AUC_{0-inf}	area under the concentration-time curve from hour 0 extrapolated to infinity
ADaM	analysis data model
AE	adverse event
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent systemic clearance
C_{max}	maximum observed plasma concentration
CRU	Clinical Research Unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
Geom CV	geometric CV
Geom Mean	geometric mean
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
λ_z	apparent terminal elimination rate constant
λ_z Lower	start of exponential fit
λ_z N	number of data points included in the log-linear regression
λ_z Span Ratio	time period over which λ_z was determined as a ratio of $t_{1/2}$
λ_z Upper	end of exponential fit
LSM	least squares mean
λ_z	apparent terminal elimination rate constant

MedDRA	Medical Dictionary for Regulatory Activities
$MRAUC_{0-24}$	ratio of paraxanthine AUC_{0-24} to caffeine AUC_{0-24}
MRT_{inf}	mean residence time extrapolated to infinity
NC	not calculated
NR	not reported
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
R^2-adj	adjusted coefficient for determination of exponential fit
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	apparent plasma terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time to maximum observed plasma concentration
V_z/F	apparent volume of distribution at the terminal phase
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 09 December 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 Objective

The primary objective of the study is to assess the effect of multiple oral doses of LOXO-305 on the PK of single oral doses of caffeine (cytochrome P450 [CYP]1A2 substrate), S-warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) in healthy subjects.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety and tolerability of multiple oral doses of LOXO-305 when administered alone, and coadministered with a single oral dose of probe drug cocktail.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of caffeine/paraxanthine, omeprazole, S-warfarin, and LOXO-305 (as appropriate):

- area under the concentration-time curve from hour 0 to 24 hours postdose (AUC_{0-24})
- area under the concentration-time curve from hour 0 to the last measurable concentration (AUC_{0-t})
- area under the concentration-time curve from hour 0 extrapolated to infinity (AUC_{0-inf})
- percentage extrapolation for AUC_{0-inf} ($\%AUC_{extrap}$)
- apparent systemic clearance (CL/F)
- apparent plasma terminal elimination half-life ($t_{1/2}$)
- maximum observed plasma concentration (C_{max})
- time to maximum observed plasma concentration (t_{max})
- apparent terminal elimination rate constant (λ_z)
- apparent volume of distribution at the terminal phase (V_z/F))
- mean residence time extrapolated to infinity (MRT_{inf})
- AUCratio of paraxanthine to caffeine ([MRAUC]; paraxanthine only).

3.2. Secondary Endpoints

Safety and tolerability will be assessed by monitoring adverse events (AEs), performing physical examinations and clinical laboratory evaluations, measuring vital signs, and recording 12-lead electrocardiograms (ECGs).

4. STUDY DESIGN

This is a Phase 1, open-label, 2-period, fixed-sequence drug-drug interaction study to investigate the effect of multiple oral doses of LOXO-305 on the PK of single oral doses of caffeine (CYP1A2 substrate) and its metabolite paraxanthine, S-warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) in healthy subjects.

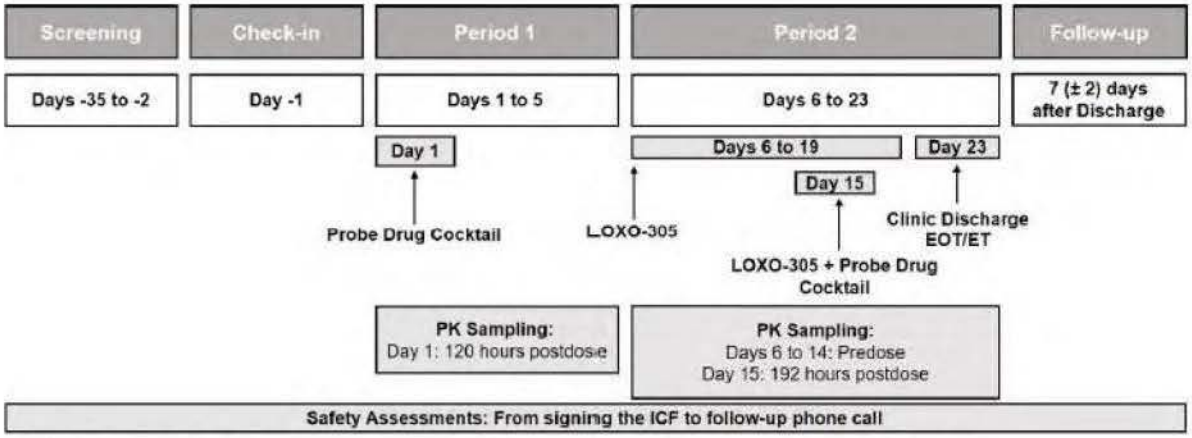
In Period 1, Day 1, 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg vitamin K (tablets), will be administered in the morning following a fast of at least 10 hours predose and 2 hours postdose. Blood samples for concentrations of the substrates (caffeine/paraxanthine, omeprazole, and S-warfarin) in plasma will be collected predose through 120 hours postdose on Day 1. Of these samples, samples will be analyzed for concentrations of caffeine/paraxanthine from predose through 24 hours postdose, for concentrations of omeprazole CCI [redacted], and for concentrations of CCI [redacted].

There will be a washout period of 5 days between administration of the probe drug cocktail on Day 1 and the first dose of LOXO-305 on Day 6.

In Period 2, on Days 6 through 19, oral doses of 200 mg LOXO-305 will be administered once daily (QD) for 14 consecutive days in the morning at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour). On Day 15, LOXO-305 will be coadministered with 200 mg caffeine (tablet), 40 mg omeprazole (capsule), and 10 mg warfarin (tablet) administered as a single dose of probe drug cocktail, along with 10 mg of vitamin K (tablets) at the actual time of the Day 1 probe drug cocktail dosing (± 1 hour) following a fast of at least 10 hours predose and 2 hours postdose. On Days 7 through 11, and Days 13, 14, 16, 18, and 19, subjects will fast for at least 2 hours predose and 1-hour postdose. On Days 6, 12, and 17 where clinical laboratory evaluations are performed, subjects will fast for at least 8 hours predose and 1 hour postdose. Blood samples for concentrations of LOXO-305 in plasma will CCI [redacted]. Samples collected CCI [redacted] LOXO-305 dosing CCI [redacted]. Blood samples for concentrations of the substrates (caffeine/paraxanthine, omeprazole, and S-warfarin) in plasma will be CCI [redacted]; of these samples, samples will be analyzed for concentrations of caffeine/paraxanthine from CCI [redacted], for concentrations of omeprazole CCI [redacted], and for concentrations of CCI [redacted].

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



EOT= end of treatment; ET = early termination; ICF = informed consent form.

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

Subjects who are determined to be screen failures are permitted to be re-screened if the Investigator (or designee), with agreement from the Sponsor, feels that the subject may meet

eligibility criteria upon re-screen. Re-screened subjects will be provided a new subject number.

To assess their eligibility to enter the study, potential subjects will be screened within 34 days (Days -35 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in).

Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 23 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Dosing of probe drug cocktail will occur on Day 1 and Day 15 and dosing of LOXO-305 will occur on Days 6 through 19. A follow-up phone call will occur for all subjects who received at least 1 dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET. The duration of participation is expected to be approximately 67 days (Screening through follow-up phone call).

In this study, physical examinations, 12-lead ECGs, vital sign measurements, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, hematology panel, urinalysis, and recording of concomitant medications will be performed at specified times during the study.

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

5. SAMPLE SIZE JUSTIFICATION

Up to CCI healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. The sample size chosen for this study was selected without statistical considerations but is consistent with previous studies of a similar design. Up to CCI subjects are anticipated to be sufficient to provide a reliable estimate of the magnitude and variability of the interaction. Replacement subjects may be enrolled only if deemed necessary by the Sponsor. Every attempt will be made to enroll at least 4 subjects of each sex in the study.

6. STUDY TREATMENTS

The study treatment sequence name and ordering to be used in the TFLs are presented in Table 1.

Table 1: Presentation of Study Treatment Sequence in TFLs

Study Treatment Sequence Label
Probe Drug Cocktail (D1-5)/ 200 mg LOXO-305 QD (D6-14)/ 200 mg LOXO-305 QD + Probe Drug Cocktail (D15-19)/ 200 mg LOXO-305 QD (D20)

QD = once daily; TFL = table, figure, and listing.

Error! Reference source not found. shows a list of the PK treatment labels and ordering that will be used in the TFLs.

Table 2: Pharmacokinetic Treatment Labels

Study Treatment Labels	Order in TFLs
200 mg caffeine	1
200 mg LOXO-305 QD + 200 mg caffeine	2
40 mg omeprazole	3
200 mg LOXO-305 QD + 40 mg omeprazole	4
10 mg warfarin	5
200 mg LOXO-305 QD + 10 mg warfarin	6
200 mg LOXO-305 QD	7

QD = once daily; TFL = table, figure, and listing.

The study treatment names and ordering to be used in the TFLs are presented in Table 3.

Table 3: Presentation of Study Treatment Labels in TFLs (Safety)

Study Treatment Labels	Order in TFLs
Probe Drug Cocktail*	1
200 mg LOXO-305 QD	2
200 mg LOXO-305 QD + Probe Drug Cocktail*	3

QD = once daily; TFL = table, figure, and listing.
*200 mg caffeine + 40 mg omeprazole + 10 mg warfarin + 10 mg Vitamin K

All treatments described above are the planned treatments. The TFLs will reflect the actual treatments received.

7. DEFINITIONS OF POPULATIONS

Any protocol deviations 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 consist of 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 consist of all subjects who have received at least 1 dose of study drug (probe cocktail drugs and/or LOXO-305). Subjects will be classified into groups based on actual treatment received.

7.3. Pharmacokinetic Population

The PK population will consist of all subjects who have received a dose of LOXO-305 or the probe cocktail drugs, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times the median t_{max}. The impact of protocol deviations on the PK population will be evaluated on a case-by-case basis.

8. STATISTICAL METHODOLOGY

8.1. General

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 EOS visit. Any subject who discontinued the study will be identified accordingly in the listings. Summaries and statistical analyses 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 1.2 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 3.1.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline and any parameter derivations.

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.
- Postdose repeats and unscheduled assessments will not be included in calculations 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 Readings

For vital signs measurements 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.

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

The baseline will be defined as the last non-missing measurement before administration of study drug on Day 1, Period 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.

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 treatment sequence will be provided, based on the all subjects population.

8.3. Screening Demographics and Baseline Characteristics

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

A summary table 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. 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

The following PK parameters will be determined where possible from the plasma concentrations of caffeine, paraxanthine, omeprazole, S-warfarin, and LOXO-305 (unless otherwise indicated) using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Parameter	Units[a]	Definition
AUC_{0-24}	h*ng/mL	area under the concentration-time curve from hour 0 to 24 hours postdose[b]
AUC_{0-t}	h*ng/mL	area under the concentration-time curve from hour 0 to the last measurable concentration (t_{last})[b]
AUC_{0-inf}	h*ng/mL	area under the concentration-time curve from hour 0 extrapolated to infinity[c] (except LOXO-305)
$\%AUC_{extrap}$	%	percentage extrapolation for AUC_{0-inf} (except LOXO-305)
C_{max}	ng/mL	maximum observed plasma concentration
t_{max}	h	time to maximum observed plasma concentration
λ_z	1/h	apparent terminal elimination rate constant (except LOXO-305)
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent systemic clearance (except paraxanthine)
V_z/F	L	apparent volume of distribution at the terminal phase (except LOXO-305 and paraxanthine)
MRT_{inf}	h	mean residence time (based on AUC_{0-inf}; except for LOXO-305)
MRAUC	NA	ratio of paraxanthine AUC to caffeine AUC (based on AUC0-24 and AUC0-48 if possible)

NA Not applicable
[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

Additional PK parameters may be determined where appropriate.

The PK analysis will be carried out where possible using 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.

The parameters C_{max} 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. 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 (λ_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 λ_z for their calculation (eg, AUC_{0-inf}, $t_{1/2}$, CL/F, V_z/F, and MRT_{inf}) 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
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj	NA	adjusted coefficient for determination of exponential fit

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

8.5.1.2. 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}.

$AUC_{0\text{-}inf}$ values where the percentage extrapolation is less than 30% will be reported. $AUC_{0\text{-}inf}$ values where the percentage extrapolation is greater than 30% will be listed but excluded from descriptive statistics.

If $AUC_{0\text{-}inf}$ cannot be determined reliably for all subjects, an alternative AUC measure, such as AUC to a fixed time point or $AUC_{0\text{-}t}$, may be used in the statistical analysis.

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

Plasma concentrations below the limit of quantification (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 concentration is missing, it may be set to 0 by default, with the exception of LOXO-305 on Day 15. If the Day 15 predose plasma concentration of LOXO-305 is missing, the Day 15 24-hour concentration may be used as the predose concentration.

8.5.1.4. 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 coefficient of variation (CV) of geometric mean will be reported as not calculated (NC).

For PK parameters the following rule will apply:

- For the calculation of summary statistics of PK parameters, all not reported (NR) and not calculated (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 3 concentrations, and/or 3 concentrations if the last is C_{max}.
- Geometric mean and CV will not be calculated for t_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by analyte and time postdose will be provided for plasma PK concentrations. All PK concentration figures will be produced on both linear and semi-logarithmic scales, with the exception of figures across all days, which will be produced on the linear scale only. The +SD bars will only be displayed on the linear scale.

Summary tables by treatment 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, caffeine, paraxanthine, omeprazole and S-warfarin

PK parameters. Excluded subjects will be listed in the PK parameter tables, but will be excluded from the statistical analysis and summary statistics and noted as such in the tables.

A statistical analysis will be conducted to investigate the drug-drug interaction on the PK of the following comparisons:

- LOXO-305 plus caffeine (test) versus caffeine alone (reference) To test the drug-drug interaction on the PK of caffeine and paraxanthine
- LOXO-305 plus omeprazole (test) versus omeprazole alone (reference)
- LOXO-305 plus warfarin (test) versus warfarin alone (reference)

The natural log-transformed[3] PK parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, and MRAUC for paraxanthine only) will be analyzed using a mixed model.[4] The model will include actual treatment as a fixed effect, and subject as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% confidence interval (CI) will be calculated; these values will then be exponentiated to give the geometric least squares mean, geometric mean ratios, and corresponding 90% CI.

Additionally, the pooled estimate (across all treatments) of the within-subject CV will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;
  by parcat1n parcat1 paramn param;
  class trtan usubjid;
  model lpk = trtan / cl residual ddfm = kr2;
  lsmeans trtan / cl pdiff = reference('1') alpha = 0.1;
  random intercept / subject = usubjid(trtseqp);
  ods output lsmeans = <data out>;
  ods output diffs = <data out>;
  ods output covparms = <data out>;
run;
```

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 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 LOXO-305 and probe drugs and vitamin K, as determined by the investigator.

The assignment of TEAEs to the treatments will be as follows:

- A TEAE occurring during or after Day 1 dosing and prior to Day 6 dosing will be assigned to Probe Drug Cocktail/or 10 mg vitamin K
- A TEAE occurring during or after Day 6 dosing and prior to Day 15 dosing will be assigned to 200 mg LOXO-305
- A TEAE occurring during or after Day 15 dosing will be assigned to 200 mg LOXO-305 + Probe Drug Cocktail/or 10 mg vitamin K

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 the last dose for TEAEs only.

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

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

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

- System organ class, preferred term, and treatment
- Preferred term and treatment

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 the first dose.
- 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 the last dose 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 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.

The observed results and change from baseline for clinical chemistry, hematology, and coagulation parameters will be summarized descriptively by 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, <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 results will be summarized descriptively by treatment 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 treatment 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. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

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

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.

3. Keene ON. The log transformation is special. *Stat Med*. 1995;14(8):811-819.

4. Brown H, Prescott R. *Applied Mixed Models in Medicine*. Chichester: John Wiley & Sons, 1999.

5. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm*. 1987;15(6):657-680.

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