Statistical Analysis Plan LOXO-BTK-20006 (J2N-OX-JZNC) Version 1.0

A Phase 1, Open Label, Two-part, Fixed-sequence Drug Interaction Study to Investigate the Effect of Strong CYP3A4 Inhibitor (Itraconazole) and CYP3A4 Inducer (Rifampin) on the Pharmacokinetics of LOXO 305 in Healthy Adult Subjects

NCT05134337

Approval date: 05-Jun-2020

Statistical Analysis Plan

A Phase 1, Open-label, Two-part, Fixed-sequence Drug Interaction Study to Investigate the Effect of Strong CYP3A4 Inhibitor (Itraconazole) and CYP3A4 Inducer (Rifampin) on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

SAP Status: Sponsor Final
SAP Version: 1
SAP Date: 05JUNE2020

Investigational Product: LOXO-305

Protocol Reference: LOXO-BTK-20006
Covance Study: 8419666

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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
AUC_{0-24}	area under the concentration-time curve from Hour 0 to 24 hours postdose
AUC_{0-inf}	AUC extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve extrapolated to infinity
BID	twice daily
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
GLSM	geometric least squares mean
GMR	geometric mean ratio
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
LLOQ	lower limit of quantification
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated

NR	no result
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time to maximum observed concentration
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1 dated 14 January 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

The primary objectives of this study are:

- To assess the impact of multiple oral doses of itraconazole (a strong cytochrome P450 [CYP]3A4 and P-glycoprotein [P-gp] inhibitor) on the single oral dose pharmacokinetics (PK) of LOXO-305 in healthy adult subjects.
- To assess the effect of multiple oral doses of rifampin (strong CYP3A4 inducer) on the single oral dose PK of LOXO-305 in healthy adult subjects.
- To assess the effect of a single oral dose of rifampin on the single oral dose PK of LOXO-305 in healthy adult subjects.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the safety and tolerability of a single oral dose of LOXO-305 when administered alone and co-administered with multiple oral doses of itraconazole.

- To assess the safety and tolerability of a single oral dose of LOXO-305 when administered alone and co-administered with single and multiple oral doses of rifampin.

3. STUDY ENDPOINTS

The following PK parameters will be calculated whenever possible, based on the plasma concentration of LOXO-305 (as appropriate):

- Area under the concentration-time curve from Hour 0 to 24 hours postdose, as calculated by the linear trapezoidal method (for Day 1 and Day 8 of Part 2 PK only [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 extrapolated to infinity (AUC_{0-inf})
- Extrapolation for area under the concentration-time curve ($\%AUC_{extrap}$)
- Maximum observed plasma concentration (C_{max})
- Time to maximum observed concentration (t_{max})
- Apparent terminal elimination rate constant (λ_Z also known as Kel)
- Apparent systemic clearance (CL/F)
- Apparent terminal elimination half-life ($t_{1/2}$)

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

4. STUDY DESIGN

This is a Phase 1, 2-part study. Each part will be conducted as an open-label, 2-period, fixed-sequence study. Following completion of the sentinel subjects in Part 1, the study parts may be conducted concurrently. Each subject will participate in either Part 1 or Part 2, but not both.

4.1. Part 1 – Itraconazole (CYP3A4 and P-gp Inhibitor)

In Part 1, Period 1, a single oral dose of 200 mg LOXO-305 will be administered in the morning of Day 1, following a fast of at least 10 hours prior to and 4 hours after dosing with LOXO-305. Blood samples for PK analysis of LOXO-305 in the absence of itraconazole will be taken up to 168 hours postdose of LOXO-305 on Day 1.

In Part 1, Period 2, multiple oral doses of 200 mg itraconazole will be administered twice daily (BID) on Day 8, and once daily (QD) from Day 9 until Day 18 inclusive (for a total of

11 consecutive days) and co-administered with a single oral dose of 200 mg LOXO-305 on Day 12 under fasted conditions. On Day 8, when itraconazole is administered BID, the morning dose will be administered alone at the actual time of the Day 1 LOXO-305 dose (± 1 hour), approximately 30 minutes after starting a standard breakfast, and the evening dose will be administered approximately 10 (±1) hours after the morning dose, approximately 30 minutes after starting a standard evening meal. All meals should be entirely consumed within 30 minutes. On Days 9 to 11 and Days 13 to 18, the QD dose of itraconazole will be administered alone at the actual time of the Day 1 LOXO-305 dose (± 1 hour), approximately 30 minutes after the start of a standard breakfast, which should be entirely consumed within 30 minutes. On Day 12, a single oral dose of 200 mg LOXO-305 and a single oral dose of 200 mg itraconazole will be co-administered in the morning, following a fast of at least 10 hours prior to and 4 hours after dosing with LOXO-305 and itraconazole. Blood samples for PK analysis of LOXO-305 in the presence of itraconazole will be taken up to 168 hours postdose of the LOXO-305 dose on Day 12.

There will be a washout period of 7 days between the dose of LOXO-305 on Day 1 (Period 1) and the first dose of itraconazole on Day 8 (Period 2).

Part 1 will be divided into 2 cohorts; a sentinel cohort will comprise 3 subjects and the second cohort will comprise 9 subjects, for a total of 12 subjects.

Following completion of the sentinel cohort, the Investigator and Sponsor will review all pertinent safety and tolerability data (and PK data, if available) from the sentinel cohort before proceeding to dose the remaining 9 subjects in the second cohort in Part 1 of subjects in Part 2.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 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 19 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. 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.

Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

4.2. Part 2 – Rifampin (CYP3A4 Inducer)

In Part 2, Period 1, a single oral dose of 200 mg LOXO-305 will be administered on Day 1, following a fast of at least 10 hours prior to and 4 hours after dosing with LOXO-305. Blood samples for PK analysis of LOXO-305 in the absence of rifampin will be taken up to 168 hours postdose of LOXO-305 on Day 1.

In Part 2, Period 2, multiple oral doses of 600 mg rifampin will be administered QD from Day 8 until Day 23 inclusive (for a total of 16 consecutive days) and co-administered with a single oral dose of 200 mg LOXO-305 on Days 8 and 17. On Days 8 and 17, a single oral dose of 200 mg LOXO-305 and a single oral dose of 600 mg rifampin will be co-administered in the morning following a fast of at least 10 hours prior to and 4 hours after

dosing with LOXO-305 and rifampin. On Days 9 to 16 and Days 18 to 23, the dose of rifampin will be administered alone at the actual time of the Day 1 LOXO-305 dose (± 1 hour), following a fast of at least 8 hours prior to and 2 hours after dosing with rifampin. Blood samples for PK analysis of LOXO-305 in the presence of rifampin will be taken up to 24 hours postdose of LOXO-305 on Day 8 and up to 168 hours postdose of LOXO-305 on Day 17.

Urine samples will be collected on Days 8, 11, 15, and 17 of Part 2 only (and stored for future potential assessment of 6β-hydroxycortisol and free cortisol concentrations to evaluate the level of CYP3A enzyme induction and/or for further exploratory analysis).

There will be a washout period of 7 days between the dose of LOXO-305 on Day 1 (Period 1) and the first dose of rifampin and dose of LOXO-305 on Day 8 (Period 2).

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the CRU on Day -1 (Check-in). Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects will be confined at the CRU from the time of Check-in (Day -1) until EOT on Day 24 upon completion of all PK and safety assessments or ET if the subject discontinues. 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.

Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

4.3 Overall

The start of the study is defined as the date the first subject who is enrolled in the study signs an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned a dose of study drug; this definition excludes screen failure subjects.

In this study, physical examinations, 12-lead ECGs, vital signs, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, creatine kinase, complete blood count, urinalysis and recording of concomitant medications will be performed at specified times during the study. The AEs and serious adverse events (SAEs) will be collected beginning at informed consent. The 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 phone call.

5. SAMPLE SIZE JUSTIFICATION

Twenty-four healthy adult male and female subjects (women of non-childbearing potential only); 12 subjects in Part 1 and 12 subjects in Part 2 to ensure that 20 subjects complete the study. This is a phase 1 study and the sample size is not based upon any formal power calculations but is consistent with previous studies of a similar design.

Each subject will participate in either Part 1 or Part 2, but not both. Part 1 will be divided into 2 cohorts; a sentinel cohort will comprise 3 subjects and the second cohort will comprise 9 subjects, for a total of 12 subjects.

Every attempt will be made to enroll at least 3 subjects of each sex in the study.

6. STUDY TREATMENTS

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

Table 1: Presentation of Study Treatment Sequences in TFLs

Part	Study Treatment Sequence	Order in TFLs
1	LOXO-305 alone/LOXO-305 and itraconazole	1
2	LOXO-305 alone/LOXO-305 and rifampin once /LOXO-305 and rifampin QD	2

The study treatment names, and ordering to be used in the TFLs are presented in Table 2 ,

Table 3. Presentation of Study Treatments in TFLs – Part 1 Non AE and PK Outputs

Study Treatment	Order in TFLs
200 mg LOXO-305 Alone	1
200 mg LOXO-305 + 200 mg itraconazole QD	2

Table 4 and Table 4.

Table 2: Presentation of Study Treatments in TFLs – Part 1 AE Outputs

Study Treatment	Order in TFLs
200 mg LOXO-305 Alone	1
200 mg itraconazole Alone	2
200 mg LOXO-305 + 200 mg itraconazole QD	3

Table 3. Presentation of Study Treatments in TFLs – Part 1 Non AE and PK Outputs

Study Treatment	Order in TFLs
200 mg LOXO-305 Alone	1
200 mg LOXO-305 + 200 mg itraconazole QD	2

Table 4: Presentation of Study Treatments in TFLs – Part 2

Study Treatment	Order in TFLs
200 mg LOXO-305 Alone	1
200 mg LOXO-305 + 600 mg rifampin once	2
200 mg LOXO-305 + 600 mg rifampin QD	3

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 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 LOXO-305, 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 and statistical analysis 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

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 end-of-treatment 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 2.2.0 (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, 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.

8.1.2. Repeat and Unscheduled Readings

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 treatment period.

Part 1

In general, baseline for Part 1 refers to the pre-dose value collected on Day 1 period 1 and Day 12. For laboratory tests, baseline is the value collected on Day -1 period 1 and Day 11 period 2.

Part 2

In general, baseline for Part 2 refers to the pre-dose value collected on Day 1 period 1, Day 8 period 2 and Day 17 Period 2.

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 period.

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 by treatment sequence 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 September 2019. 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 LOXO-305 using non-compartmental methods performed using Phoenix WinNonlin (Certara USA, Inc.) version 8.1 or higher:

Parameter	Definition
AUC_{0-24}	area under the concentration-time curve from Hour 0 to 24 hours postdose, as calculated by the linear trapezoidal rule for increasing and decreasing concentrations (for Day 1 and Day 8 of Part 2 PK only)
AUC_{0-t}	area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
AUC_{0-inf}	AUC extrapolated to infinity, calculated using the formula: $AUC_{0-inf} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage extrapolation for AUC_{0-inf} (except for Part 2 Day 8)
C_{max}	maximum observed plasma concentration
t_{max}	time to maximum observed plasma concentration
λz	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; additionally, the number of points used to estimate λ_z will be presented in a listing (wherever possible)
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (ln)(2)/λ_Z
CL/F	apparent systemic clearance (except for Part 2 Day 8)

Additional PK parameters may be determined where appropriate. The number of points used to estimate λ_Z, the lower and upper points used in estimation, λ_Z span ratio, and the adjusted coefficient for determination of exponential fit (R^2 adjusted) will be presented in a listing.

The PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data. 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.

No value for λ_Z, $AUC_{0\text{-inf}}$, CL/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log linear phase in the concentration-time profile. The PK sampling to 24 hours on Day 8 in Part 2 may not be sufficient for calculation of several λ_Z-dependent PK parameters.

No PK parameters will be calculated for subjects with 2 or fewer consecutive timepoints with quantifiable concentrations.

C_{max} and t_{max} will be obtained directly from the plasma 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 if possible.

8.5.1.1. 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 Period 1 predose concentration is missing, it may be set to 0 (for PK analysis only) by default within the Phoenix WinNonlin software. Handling of missing predose values in Period 2 will be assessed on a case by case basis.

8.5.1.2. Criteria for the Calculation of an Apparent Terminal Elimination Rate Constant and Half-Life

8.5.1.2.1. Number of Data Points

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

8.5.1.2.2. Goodness of Fit

When assessing terminal elimination phases, the adjusted coefficient of determination for exponential fit (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 (eg, $AUC_{0\text{-}inf}$, λ_z, $t_{1/2}$, and CL/F) will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

8.5.1.2.3. Period of Estimation

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

Where the terminal elimination rate constant is estimated over a time period of less than 2 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 CSR.

8.5.1.3. Calculation of AUC

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following 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.

$AUC_{0\text{-}inf}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0\text{-}inf}$ values where the percentage extrapolation is between 20 to 30% will be flagged, and included in the summary statistics and statistical analysis, whilst $AUC_{0\text{-}inf}$ values where the percentage extrapolation is greater than 30% will be reported but excluded from summary statistics and statistical analysis.

8.5.1.4. 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 the CSR.

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

Subjects with positive predose values greater than 5% of Cmax may be excluded from the summary statistics and statistical analysis at the discretion of the Pharmacokineticist.

8.5.2. Presentation of Pharmacokinetic Data

8.5.2.1. Presentation Pharmacokinetic Plasma Drug Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (eg, no result [NR]) in 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 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). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic standard deviation (SD), median, minimum and maximum will be presented as zero, and the geometric mean and geometric coefficient of variation (CV) will be denoted as NC.
- If the value of the arithmetic mean or median is below the LLOQ, these values will be presented as zero and the geometric mean and geometric CV will be denoted as NC.

8.5.2.2. Presentation 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 3 concentrations, and/or 3 concentrations if the last is C_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (+ SD) figures, overlaying individual figures, and individual figures by treatment 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 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.

8.5.3.1. Statistical Analyses

A statistical analysis will be conducted to investigate the drug-drug interaction on the PK of LOXO-305 for AUC_{0-24} ,AUC_{0-t}, AUC_{0-inf}, and C_{max} . The comparisons of interest are:

Study Part 1:

To access the impact of multiple oral doses of itraconazole on the single oral dose PK of LOXO-305 (AUC_{0-t}, AUC_{0-inf}, and C_{max})

- 200 mg itraconazole co-administered with 200 mg LOXO-305 (test treatment) vs 200 mg LOXO-305 alone (reference treatment).

Study Part 2:

To assess the effect of multiple oral doses of rifampin (strong CYP3A4 inducer) on the single oral dose PK of LOXO-305 (AUC_{0-t}, AUC_{0-inf}, and C_{max}) in healthy adult subjects

- 600 mg rifampin QD co-administered with 200 mg LOXO-305 (test treatment, Day 17) vs 200 mg LOXO-305 alone (reference treatment)

To assess the effect of a single oral dose of rifampin on the single oral dose PK of LOXO-305 (AUC_{0-24}, and C_{max})

- 600 mg rifampin once co-administered with 200 mg LOXO-305 (test treatment, Day 8) vs 200 mg LOXO-305 alone (reference treatment)

The ln-transformed[3] PK parameters (AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, and C_{max}) will be analyzed using a mixed model.[4] The model will include actual treatment as 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 (GLSM), geometric mean ratios (GMR), 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 = kr;
  lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
  random intercept / subject = usubjid;
```

```
  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 22.1. 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 (LOXO-305 or itraconazole or rifampin), as determined by the investigator.

For Part 1 of this study, the assignment of TEAEs to the associated treatments will be as follows:

- A TEAE occurring during or after Day 1 dosing and prior to Day 8 dosing will be assigned to 200 mg LOXO-305
- A TEAE occurring during or after Day 8 dosing and prior to Day 12 dosing will be assigned to 200 mg itraconazole
- A TEAE occurring during or after Day 12 dosing will be assigned to 200 mg LOXO-305 and/or 200 mg itraconazole

For Part 2 of this study, the assignment of TEAEs to the associated treatments will be as follows:

- A TEAE occurring during or after Day 1 dosing and prior to Day 8 dosing will be assigned to 200 mg LOXO-305
- A TEAE occurring during or after Day 8 dosing will be assigned to 200 mg LOXO-305 and/or 600 mg rifampin

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, and leading to discontinuation) by treatment
- TEAEs by severity and treatment

- Treatment-related TEAEs (overall, serious, and leading to discontinuation) 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
- System organ class, preferred term, day of onset, 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 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, complete blood count, and coagulation parameters will be summarized descriptively by study part and timepoint. Boxplots of the observed values will also be provided.

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 treatment and timepoint. Boxplots of the observed values will also be provided.

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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 group and timepoint. Boxplots of the observed values will also be provided. 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