Statistical Analysis Plan LOXO-BTK-20009

A Phase I, Open-Label, Randomized, 2-Way Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of Pirtobrutinib (LOXO-305) in Healthy Subjects

NCT06180980

Approval date: 11-May-2021

Statistical Analysis Plan

A Phase I, Open-Label, Randomized, 2-Way Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of LOXO-305 in Healthy Subjects

SAP Status: Sponsor Final
SAP Version: 2.0
SAP Date: 11MAY2021

Investigational Product: LOXO-305

Protocol Reference: LOXO-BTK-20009
Covance Study: 8419688

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.
1900 Mason Avenue, Suite 140
Daytona Beach, FL 32117
USA

Up to 2 additional sites in the United States may be utilized.

Coordinating Investigator:
PPD

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

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

$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve extrapolated to infinity
ADaM	analysis data model
AE	adverse event
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from hour 0 to 24 hours postdose
AUC_{0-inf}	area under the concentration-time curve from hour 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
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
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
MedDRA	Medical Dictionary for Regulatory Activities

MRT_{inf}	mean residence time based on area under the concentration-time curve from time 0 extrapolated to infinity
NC	not calculated
NR	not reported
PK	pharmacokinetic(s)
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(s)
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TFL	Table, figure, and listing
$t_{1/2}$	apparent plasma terminal elimination half-life
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 1 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

2.1.1. Primary Objective

The primary objective of the study is to assess the effect of food on the PK of a single oral dose of LOXO-305 under fasted and fed conditions in healthy adult subjects.

2.1.2. Secondary Objective

The secondary objective of the study is to assess the safety and tolerability of a single oral dose of LOXO-305 with and without food in healthy adult subjects.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

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

- area under the concentration-time curve (AUC) 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)

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, randomized, 2-way crossover study to investigate the effect of food on the single oral dose PK of LOXO-305 in healthy adult subjects.

A single oral dose of LOXO-305 will be administered under fasted conditions (Treatment A) and fed conditions (Treatment B). PK sampling will be obtained for 168 hours after administration of each dose of LOXO-305 (ie, on Days 1 and 8). The 2 treatment sequences will be AB and BA. Subjects will be randomly assigned to 1 of the 2 treatment sequences, according to a randomization scheme issued by Covance. Up to 20 healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled.

In Treatment A, a single oral dose of 200 mg LOXO-305 will be administered in the morning on Day 1 or Day 8 (according to the randomization scheme), following a fast of at least 10 hours prior to and 4 hours after dosing. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose administration.

In Treatment B, a single oral dose of 200 mg LOXO-305 will be administered in the morning on Day 1 or Day 8 (according to the randomization scheme), approximately 30 minutes after starting a high-fat breakfast. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose administration. High-fat breakfasts should be entirely consumed within 30 minutes.

Blood samples for the analysis of plasma concentrations of LOXO-305 will be collected from predose through 168 hours postdose for Treatment A and Treatment B.

There will be a washout period of 7 days between the doses of LOXO-305 administered in Treatments A and B.

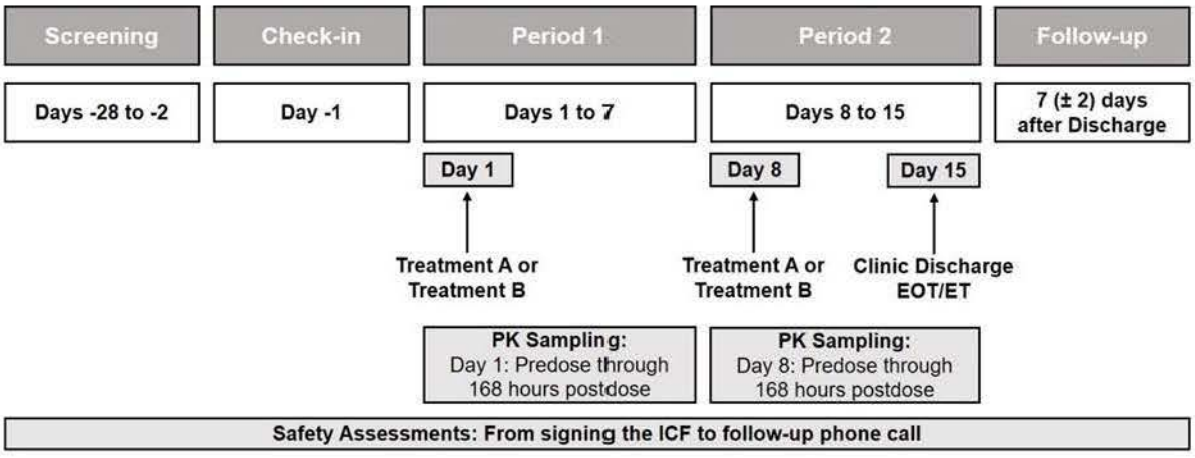
A schematic of the study design is presented in Figure 1. The start of the study is defined as the date the first subject who is enrolled in the study signed an Informed Consent Form (ICF). Note that enrolled subjects are defined as those subjects who are assigned to receive a dose of study drug; this 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 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 15 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Subjects will be dosed on Day 1 and Day 8. 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 53 days (Screening through follow-up phone call).

Figure 1: Study Design



Abbreviations: EOT = End of Treatment; ET = Early Termination; ICF = Informed Consent Form; PK = pharmacokinetic.

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 specific 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

Up to CCI healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. This is a Phase 1 study and the sample size 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 food effect. The highest within-subject coefficient of variation (CV) observed in LOXO-BTK-20014 was CCI for C_{max}. A sample size of CCI will provide approximately 80% power to have the respective 90% confidence intervals (CIs) for the geometric mean ratios for C_{max} and AUC values between fed and fasted treatments are within the interval of 80.00% to 125.00%, assuming a within-subject CV of CCI and that the expected ratio of means is CCI. Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

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

6. STUDY TREATMENTS

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

Table 1: Presentation of Study Treatments in TFLs

Study Treatment	Abbreviation	Order in TFLs
200 mg LOXO-305 (Fasted)	A	1
200 mg LOXO-305 (Fed)	B	2

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

Table 2: Presentation of Study Treatment Sequences in TFLs

Study Treatment Sequence	Abbreviation	Order in TFLs
200 mg LOXO-305 (Fasted) on Day 1/ 200 mg LOXO-305 (Fed) on Day 8/	AB	1
200 mg LOXO-305 (Fed) on Day 1/ 200 mg LOXO-305 (Fasted) on Day 8/	BA	2

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

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 consist of all subjects who have received at least 1 dose of 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 1 dose of LOXO-305, 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 EOT 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.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation and 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 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 Readings

For vital sign 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 postdose. 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.

Postdose repeats, unscheduled values, 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 on Day 1 and Day 8.

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 on Day 1 and Day 8.

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.

8.1.4. Period Specific Study Day

Period specific study day is defined as per Table 3 for ECG and Vital signs and Table 4 for clinical laboratory parameters.

Table 3: ECG and Vitals Study day

Period	Period Specific Study Day							
	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	1 (pre-dose)	1 (post dose)	2	3	4	5	6	7
2	8 (pre-dose)	8 (post dose)	9	10	11	12	13	14

Table 4: Clinical laboratory parameters Study day

Period	Period Specific Study Day						
	Baseline	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	Day -1			4			7*
2	Day 7 Period 1			10			14

*Day 7 measurements will be summarized at day 7 for period 1 used as baselines for the period 2.

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. Demographics

The demographics 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. 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 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 LOXO-305 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Parameter	Units[a]	Definition
AUC_{0-t}	h*ng/mL	area under the concentration-time curve from hour 0 to the last measurable concentration (t_{last})[b]
AUC_{0-24}	h*ng/mL	area under the concentration-time curve from hour 0 to 24 hours postdose[b]
AUC_{0-inf}	h*ng/mL	area under the concentration-time curve from hour 0 extrapolated to infinity[c]
$\%AUC_{extrap}$	%	percentage extrapolation for AUC_{0-inf}
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
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent systemic clearance
V_z/F	L	apparent volume of distribution at terminal phase
MRT_{inf}	h	mean residence time (based on AUC_{0-inf})

[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) 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 and statistical analysis.

If $AUC_{0\text{-}inf}$ cannot be determined reliably for all subjects and/or treatments, an alternative AUC measure, such as $AUC_{0\text{-}t}$, may be used in the statistical analysis for food effect.

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 Day 1 or Day 8 predose plasma concentration is missing, it may be set to 0 by default within Phoenix WinNonlin.

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 for LOXO-305 on Day 1 will be considered anomalous and set to missing for the PK analysis.

If the predose concentration is >5% of C_{max} in the second period, all PK concentration and parameter data will be excluded from the summary statistics and statistical analysis for that period.

8.5.1.5. 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).

8.5.2. Presentation Pharmacokinetic Parameters

- 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}.

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 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. 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; geometric mean and CV will not be calculated for t_{max}. 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.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final CSR.

8.5.3.1. Statistical Analyses

A statistical analysis will be conducted to investigate the food effect on the treatment by comparing Treatment B (Fed) to Treatment A (Fasted) for AUC_{0-t}, AUC_{0-inf}, and C_{max}, using Treatment A as reference.

The natural log (ln)-transformed[3] PK parameters will be analyzed using a mixed model.[4] The model will include planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the fed and fasted treatments, and corresponding 90% CIs will be calculated; these values will then be back-transformed to give the geometric least square mean (GLSM), ratio of GLSMs, and corresponding 90% CIs.

For each PK parameter separately, it will be concluded that there is absence of a food effect on the treatment if the 90% CI for the ratio of GLSMs is completely contained within the predefined interval of (80.00%, 125.00%). This procedure is equivalent to Schuirmann's[5] two one-sided tests at the 0.05 level of significance.

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

Example of the SAS code that will be used is as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;
class trtan aperiod trtseqp usubjid;
 model lpk = trtan aperiod trtseqp / cl residual ddfm = kr;
 lsmeans trtan / cl pdiff = control('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 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 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. 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 treatment and period specific 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 Results

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 period specific 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 period specific 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.
Final Version 2.0	11MAY2021	Period added as fixed effect to mixed model to correspond with the 2x2 study design. This was implemented prior to database lock.

NA = not applicable