Statistical Analysis Plan Version 2.0 J2G-OX-JZJL

An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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16.1.9. Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H2 Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

Statistical Analysis Plan Status: Final 2
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Study Drug: LOXO-292

Sponsor Reference Number: LOXO-RET-19075
Covance Study Number: 8412056

Clinical Phase 1

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PPD

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

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

Covance approval:

PPD

PPD

Sponsor approval:

PPD

PPD

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3 ABBREVIATIONS

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

ADaM	analysis data model
AE	adverse event
ANOVA	analysis of variance
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of last quantifiable concentration
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
BID	twice daily
BLQ	below the level of quantification
CDISC	Clinical Data Interchange Standards Consortium
CL/F	apparent systemic clearance
C_{max}	maximum observed concentration
CSR	clinical study report
CV%	coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
λ_z	apparent terminal elimination rate constant
LLOQ	lower limit of quantification
LSM	least squares means
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated
NR	no result
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
QD	every day
QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction
SAE	serious Adverse Event
SAP	Statistical Analysis Plan

$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of maximum observed concentration
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
V_z/F	apparent volume of distribution

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1 dated 20 June 2019).

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

The intent of this document is to provide guidance for the statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Loxo Oncology, Inc. and Company. A limited amount of information concerning 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 agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon 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 entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

5.1 Primary Objectives:

- To assess the effect of multiple doses of an H2 antagonist (ranitidine) administered with a single dose of LOXO-292 on the PK of LOXO-292 under fasted conditions in healthy adult subjects.
- To assess the effect of multiple doses of a PPI (omeprazole) administered with a single dose of LOXO-292 on the PK of LOXO-292 given with a low-fat meal in healthy adult subjects.

5.2 Secondary Objective:

- To determine the safety and tolerability of a single dose of LOXO-292 under fasted conditions alone, in combination with an H2 antagonist (ranitidine) under fasted conditions, and in combination with a PPI (omeprazole) given with a low-fat meal in healthy adult subjects.

6 STUDY DESIGN

This is an open label, 3-period, fixed sequence study.

In Period 1, a single oral dose of LOXO-292 will be administered under fasted conditions. On Day 1 of Period 1, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 1.

In Period 2, multiple oral doses of ranitidine will be administered twice daily from Day 8 until Day 18 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 12 under fasted conditions. On Day 12, a single oral dose of 160 mg of LOXO-292 will be administered following a fast of 10 hours prior to and 4 hours after the LOXO-292 dose. On Day 12, ranitidine will be administered 2 hours (± 10 minutes) after the LOXO-292 dose. On Days 8-11 and 13-18, the morning dose of ranitidine will be administered (with breakfast) approximately 2 hours (± 1 hour) after the planned or actual time of the Day 12 LOXO-292 dose and the evening dose of ranitidine will be administered (with a light meal/snack) approximately 10 hours (± 1 hour) prior to the planned or actual time of the Day 12 LOXO-292 dose. Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 12.

In Period 3, multiple oral doses of omeprazole will be administered once daily from Day 19 until Day 29 inclusively (for a total of 11 consecutive days) and administered with a single oral dose of LOXO-292 on Day 23 with a low-fat meal. On Day 23, omeprazole and a single oral dose of 160 mg of LOXO-292 will be coadministered within 30 minutes of the start of a low-fat meal, which will be entirely consumed within 30 minutes. On Days 19-22 and 24-29, omeprazole will be administered following a fast of 2 hours prior to and 1 hour after the omeprazole dose (Note: omeprazole will be administered at approximately the actual time of the Day 12 LOXO-292 dosing). Blood samples for LOXO-292 PK analysis will be taken for 168 hours after the LOXO-292 dose on Day 23.

There will be a washout period of 7 days between the LOXO-292 dose in Period 1 and the first dose of ranitidine in Period 2 and a washout period of 7 days between the LOXO-292 dose in Period 2 and the first dose of omeprazole in Period 3.

7 TREATMENTS

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

Study Treatment labels	**Treatment Order on TFLs**
Treatment sequence label	
160 mg LOXO-292/ 160 mg LOXO-292 + 150 mg ranitidine BID/ 160 mg LOXO-292 + 40 mg omeprazole QD	
Treatment labels	
160 mg LOXO-292	1
150 mg ranitidine BID	2
160 mg LOXO-292 + 150 mg ranitidine BID	3
40 mg omeprazole QD	4
160 mg LOXO-292 + 40 mg omeprazole QD	5
PK outputs	
160 mg LOXO-292 (fasted)	1
160 mg LOXO-292 (fasted) + 150 mg ranitidine BID	2
160 mg LOXO-292 (fed) + 40 mg omeprazole QD	3

8 SAMPLE SIZE JUSTIFICATION

CCI [redacted]

9 DEFINITION OF ANALYSIS POPULATIONS

The **All Subjects Population** will consist of any subjects who signed informed consent and had study assessments recorded on the database as per the protocol.

The **Safety Population** will consist of all subjects who received at least 1 dose of LOXO-292.

The **Pharmacokinetic Population** will consist of all subjects who received a dose of LOXO-292, 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 adverse event (AE) of vomiting that occurs at or before 2 times median time to maximum concentration.

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

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK).

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

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4.

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

10.1.1 Definition of Baseline and Change from Baseline

Baseline value is defined as the last non-missing measurement prior to the administration of LOXO-292 in each period, including repeats (vital signs and electrocardiograms [ECGs]) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings). LOXO-292 dosing days are: Day 1 (Period 1), Day 12 (Period 2) and Day 23 (Period 3).

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

values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

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

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Subject Disposition

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

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of LOXO-292 using non-compartmental methods performed using Phoenix WinNonlin (Certara USA, Inc.) version 8.1 or higher:

Parameter	Definition
AUC_{0-t}	Area under the concentration-time curve from time 0 to the time of last quantifiable concentration (T_{last})[a]
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity[a]
$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	Maximum observed concentration
t_{max}	Time of maximum observed concentration
λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{1/2}$	Apparent terminal elimination half-life
CL/F	Apparent systemic clearance
V_z/F	Apparent volume of distribution

Note: Additionally, the number of points used to determine λ_z, upper and lower limits of data selection, and coefficient of determination of exponential fit (R^2) will be presented in a listing.

[a] All AUCs will be calculated using the linear trapezoidal rule for both increasing and decreasing concentrations.

Additional PK parameters may be determined where appropriate.

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.

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.

Criteria for handling concentrations below the limit of quantification in Pharmacokinetic analysis

Concentration values that are below the level 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 will be set to 0 (for PK analysis only) by default within the Phoenix WinNonlin software. Handling of missing predose values in Periods 2 and 3 will be assessed on a case by case basis.

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

Number of Data Points

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

Goodness of Fit

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

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

Period of Estimation

The span of time used in determination of the elimination rate constant will be greater than two half-lives, where possible.

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

Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ) with at least one of these concentrations following C_{max}.
- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is between 20 to 30% will be reported, flagged, and included in the descriptive statistics, whilst $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be reported but excluded from descriptive statistics.

Anomalous Values

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

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

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

10.3.2 Presentation of Pharmacokinetic Data

Presentation of 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 a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are less than three values in the data series, only the minimum, maximum and number of subjects 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 CV%, aarithmetic standard deviation, median, minimum and maximum will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

Presentation of Pharmacokinetic Parameters

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

The AUC values will be set to NC if they did not meet minimum data requirements for calculation.

10.3.3 Pharmacokinetic Statistical Methodology

A statistical analysis will be conducted to investigate the drug-drug interaction on the PK of LOXO-292 for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The comparisons of interest are:

- LOXO-292 (fasted) co-administered with ranitidine vs LOXO-292 (fasted)
- LOXO-292 (fed) co-administered with omeprazole vs LOXO-292 (fasted)

The primary analysis planned for this study is an Analysis of Variance (ANOVA) model that includes treatment as a fixed-effect and subject as a random-effect. CCI [redacted]

10.4 Safety and Tolerability Assessments

10.4.1 Adverse Events

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

A TEAE occurring during or after Day 1 dosing and up to predose Day 8 will be assigned to treatment 160 mg LOXO-292. A TEAE occurring after Day 8 dosing and up to Day 11 will be assigned to 150 mg ranitidine. A TEAE occurring after Day 12 dosing and up to Day 19 predose will be assigned to 160 mg LOXO-292 + 150 mg ranitidine. A TEAE occurring after Day 19 dosing and predose Day 22 will be assigned to 40 mg omeprazole QD. A TEAE occurring after Day 23 dosing until Follow-up will be assigned to 160 mg LOXO-292 + 40 mg omeprazole QD.

All AEs will be listed. The TEAEs will be summarized by treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarized by treatment, and by Medical Dictionary for Regulatory Activities system organ class and preferred term. A frequency summary will be presented by day of onset across the multiple-dosing period. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of "Related"). Any severe or serious AEs will be tabulated. For any AEs that change severity ratings for a given treatment, the AE will be included only once under the maximum severity rating in the summaries. If a TEAE decreases in severity grade, the new TEAE record with lesser severity will be counted as the same TEAE event of the previous record with worse severity under the same treatment group. Onset times postdose are calculated from the last dose administered. Discontinuations due to AEs will be listed.

10.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization drug dictionary (WHODrug Global B3, 01 March 2019). Concomitant medication will be listed.

10.4.3 Clinical Laboratory Parameters

Clinical chemistry, hematology and coagulation data will be summarized by parameter and treatment, together with changes from baseline. In addition, all clinical chemistry, hematology, coagulation and urinalysis data outside the clinical reference ranges will be listed by parameter and treatment.

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

10.4.4 Vital Signs

The vital signs data will be summarized by treatment, together with changes from baseline. Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings.

10.4.5 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG tracings These data include the QT interval calculated using the Fridericia correction (QTcF), the PR, RR and QT intervals, the QRS duration, and heart rate.

Changes from baseline will be calculated. Values for ECG parameters outside the clinical reference ranges will be flagged, including QTcF > 450 msec and change from baseline > 30 msec, on the individual subject data listings.

The ECG data will be summarized and listed by treatment, together with changes from baseline.

10.4.6 Other Assessments

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

10.4.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned

11 INTERIM ANALYSES

No interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

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

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

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

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.