

LOXO-BTK-20014 Statistical Analysis Plan Version 2.0

A Phase 1, Open Label, Randomized, 2-Way Crossover, 3-Period Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

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Statistical Analysis Plan

A Phase 1, Open-label, Randomized, 2-Way Crossover, 3-Period Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

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Information described herein is confidential and may be disclosed only with the express written permission of the sponsor.

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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-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
AUC _{0-inf}	AUC extrapolated to infinity
%AUC _{extrap}	percentage extrapolation for area under the concentration-time curve extrapolated to infinity
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
GLSM	geometric least squares 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
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated
NR	no result
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
SAE	serious adverse event
SAP	statistical analysis plan

SD	standard deviation
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
$t_{1/2}$	apparent terminal elimination half-life
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 2.0 dated 29 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

The primary objectives of the study are:

- to assess the effect of food on the PK of LOXO-305 administered under fasted conditions and after a standard meal in healthy adult subjects
- to assess the effect of a gastric pH change on the PK of LOXO-305 after multiple-doses of a proton pump inhibitor (PPI) (omeprazole) in healthy adult subjects.

The secondary objective of the study is:

- to determine the safety and tolerability of a single dose of LOXO-305 administered with and without food and in the presence of a PPI (omeprazole) in healthy adult subjects.

3. STUDY 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 from Hour 0 to 24 hours postdose, as calculated by the linear trapezoidal method (AUC₀₋₂₄)

- 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)
- 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, open-label, randomized, 2-way crossover, 3-period study. A single oral dose of LOXO-305 will be administered under fasted conditions (Treatment A) and fed conditions (Treatment B). Multiple oral doses of omeprazole will be administered once daily from Day 15 through Day 18, with a single oral dose of LOXO-305 co-administered with omeprazole under fasted conditions on Day 18 (Treatment C). PK sampling will be obtained for 168 hours after administration of each dose of LOXO-305 (ie, on Days 1, 8, and 18). The 2 treatment sequences will be ABC and BAC. Subjects will be randomly assigned to 1 of the 2 treatment sequences, according to a randomization scheme issued by Covance.

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. 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 standard breakfast. In Treatment C, a single oral dose of 40 mg omeprazole will be administered in the morning on Days 15, 16 and 17, following a fast of at least 8 hours prior to omeprazole dosing, followed by a standard breakfast administered approximately 1 hour after dosing. On Day 18, a single oral dose of 40 mg omeprazole will be co-administered with a single oral dose of 200 mg LOXO-305 in the morning, following a fast of at least 10 hours prior to and 4 hours after omeprazole and LOXO-305 co-administration. Standard breakfasts should be entirely consumed within 30 minutes. Serial PK blood samples for the analysis of plasma concentrations of LOXO-305 will be collected from predose through 168 hours postdose for each treatment.

There will be a washout period of 7 days between the doses of LOXO-305 administered in Treatments A and B, and a washout period of 7 days between the doses of LOXO-305 administered in Treatments A or B and the first dose of omeprazole in Treatment C.

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). 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 End of Treatment (EOT) on Day 25 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 (\pm 2 days) after EOT or ET.

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

CCI [REDACTED] 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.

Every attempt will be made to enroll at least 2 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
200 mg LOXO-305 + 40 mg Omeprazole (Fasted)	C	3
40 mg Omeprazole alone (Fasted)	OMP alone	4

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/ 40 mg Omeprazole (Fasted) on Days 15 to 17/ 200 mg LOXO-305 + 40 mg Omeprazole (Fasted) on Day 18	A/B/C	1
200 mg LOXO-305 (Fed) on Day 1/ 200 mg LOXO-305 (Fasted) on Day 8/ 40 mg Omeprazole (Fasted) on Days 15 to 17/ 200 mg LOXO-305 + 40 mg Omeprazole (Fasted) on Day 18	B/A/C	2

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 Early Termination measurements are 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. In general, baseline refers to the pre-dose value collected on Day 1 Treatment A or B, Day 8 Treatment A or B, and Day 18 Treatment C. For laboratory tests, baseline is the value collected on Day -1 Treatment A or B, Day 7 Treatment A or B, and Day 17 Treatment C.. 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 the last dose.

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. 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
C_{\max}	maximum observed plasma concentration
t_{\max}	time to maximum observed concentration
AUC_{0-24}	area under the concentration-time curve (AUC) from Hour 0 to 24 hours postdose, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
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
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant
%AUC _{extrap}	percentage extrapolation for $AUC_{0-\infty}$
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 (whenever possible), where $t_{1/2} = \ln(2)/\lambda_z$
CL/F	apparent systemic clearance

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.

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.

8.5.1.1. 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 predose concentration is missing, it may be set to zero in PK analysis by default within Phoenix WinNonlin.

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) 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 , $t_{1/2}$, 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, with at least one of these concentrations following C_{\max} .

For any partial AUC determination (eg. AUC_{0-24}), 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 >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 >5% of C_{\max} 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 lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV will be denoted as NC.

8.5.3. 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} .

8.5.4. 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.

8.5.4.1. Statistical Analyses

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

- 200 mg LOXO-305 (Fed) (test treatment) vs '200 mg LOXO-305 (Fasted) (reference treatment) i.e. Treatment B Vs Treatment A
- 200 mg LOXO-305 + 40 mg Omeprazole (Fasted) (test treatment) vs 200 mg LOXO-305 (Fasted) (reference treatment) i.e. Treatment C Vs Treatment A

The natural log (ln)-transformed³ PK parameters will be analyzed using a mixed model.⁴ The model will include planned treatment sequence, 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% confidence interval (CI) will be calculated; these values will then be exponentiated to give the geometric least square means (GLSM), geometric mean ratios (GMR), and corresponding 90% CIs.

This procedure is equivalent to Schuirmann's⁵ two one-sided tests at the 0.05 level of significance.

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.

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

Mixed Model Analysis

CCI



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 Omeprazole), as determined by the investigator.

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 (Fasted)' or '200 mg LOXO-305 (Fed)' depending on the subject's fasting status prior to Day 1 dosing.

- A TEAE occurring during or after Day 8 dosing and prior to Day 15 dosing will be assigned to '200 mg LOXO-305 (Fasted)' or '200 mg LOXO-305 (Fed)' depending on the subject's fasting status prior to Day 8 dosing.
- A TEAE occurring during or after Day 15 dosing and prior to Day 18 dosing will be assigned to '40 mg Omeprazole (Fasted)'.
- A TEAE occurring during or after Day 18 dosing will be assigned to '200 mg LOXO-305 + 40 mg Omeprazole (Fasted)'.

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

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 inferential statistical 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.
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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	21MAY2020	Update wording in sections 8.6.2-8.6.4 to make clear that summary tables to include changes from baseline. Removed referencing of upversioning for MEDRA and CTCAE as same versions will be used throughout study.

NA = not applicable