Statistical Analysis Plan J2N-OX-JZNS Version 1.0

A Phase I, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-305 in Healthy Adult Subjects

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Statistical Analysis Plan

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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	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 time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve extrapolated to infinity
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
GLSM	Geometric least square mean
Geom Mean	Geometric mean
GMR	Geometric mean ratio
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
λ_Z	apparent terminal elimination rate constant
ln	natural log
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities

NC	not calculated
NR	No result
PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	apparent plasma terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time to maximum observed plasma concentration
V_z/F	apparent volume of distribution at 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 04 August 2020) and electronic case report form.

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

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Loxo Oncology, Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Loxo Oncology, Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective of the study is:

- To assess the safety and tolerability of single oral doses of LOXO-305 when administered to healthy adult subjects.

2.2. Secondary Objectives

The secondary objective of the study is:

- To assess the PK of single oral doses of LOXO-305 when administered to healthy adult subjects.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

Safety

The primary endpoint of this study is to assess the safety and tolerability of LOXO-305 at single doses ≥ 300 mg. This study will investigate the safety and tolerability of single doses (ie, potential therapeutic and supratherapeutic exposures) of LOXO-305 when administered to healthy subjects. Ascending doses up to and possibly including 900 mg will be investigated.

Safety and tolerability will be assessed by monitoring adverse events (AEs) and concomitant medications, performing physical examinations and clinical laboratory evaluations, measuring vital signs, and performing 12-lead electrocardiograms (ECGs). These safety and tolerability endpoints are deemed adequate to detect any safety signals when the planned dose range of LOXO-305 is administered to healthy subjects.

3.2. Secondary Endpoints

PK

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 (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} ($\%AUC_{extrap}$)
- maximum observed plasma concentration (C_{max})
- time to maximum observed plasma concentration (t_{max})
- apparent terminal elimination rate constant (λ_Z)
- apparent systemic clearance (CL/F)
- apparent volume of distribution at terminal phase (V_Z/F)
- apparent plasma terminal elimination half-life ($t_{1/2}$).

4. STUDY DESIGN

This is an open-label, single-ascending dose study to evaluate the safety, tolerability, and PK of LOXO-305.

Up to 4 cohorts are planned for evaluation. In each cohort, 6 healthy adult subjects are planned for evaluation. Subjects will participate in only 1 cohort. In each cohort, subjects will receive a single oral dose of LOXO-305 on Day 1. Each cohort will include a sentinel group

of 2 subjects which will be dosed at least 48 hours before the remaining 4 subjects (following review of available safety data).

A single oral dose of LOXO-305 will be administered on Day 1 for each cohort as follows:

- Cohort 1 (Treatment A): 300 mg
- Cohort 2 (Treatment B): up to 600 mg
- Cohort 3 (Treatment C): up to 900 mg

One additional cohort (6 subjects) may be enrolled if it is deemed appropriate to repeat any dose level, or to add an interim dose level or levels (equal to or lower than 900 mg), as determined by the Sponsor in consultation with the Investigator (or designee), depending on the safety, tolerability, and PK results from the prior cohort(s). Dosing will not exceed 900 mg in any subject, nor will any subject be given a dose for which the C_{max} would exceed 26,000 ng/mL.

Dose escalation to a higher dose level (ie, next cohort) will not take place until the Investigator (or designee) and the Sponsor have reviewed all pertinent safety/tolerability data (ie, physical examinations, 12-lead ECGs, vital sign measurements, clinical laboratory evaluations, and AEs) through a minimum of 168 hours (Day 8) and have determined that adequate safety and tolerability from the previous lower dose cohort has been demonstrated to permit proceeding to the next cohort. PK data through at least 72 hours (approximately 3 half-lives) after dosing will be reviewed to guide the dose-escalation decision. Data from a minimum of 4 subjects will be reviewed in order to make a dose escalation decision. Each cohort will include a sentinel group of 2 subjects will be dosed at least 48 hours before the remaining 4 subjects (following review of all available safety data).

Each treatment (A, B, and C) will be administered orally in the morning following a fast of at least 10 hours prior to and 4 hours after dosing.

The PK sampling will be obtained for 168 hours after administration of each dose of LOXO-305.

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 8 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 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 46 days (Screening through follow-up phone call).

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

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. Study completion is defined as the time of the last subject's follow-up phone call.

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

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

5. SAMPLE SIZE JUSTIFICATION

This study is planned to enroll up to 24 healthy adult male and female subjects (women of non-childbearing potential only). Six subjects will participate in each cohort.

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

Every attempt will be made to enroll at least 1 subject of each sex in each cohort.

No formal statistical assessment of sample size has been conducted. The sample size chosen for this study is common in single-ascending dose studies and is considered sufficient to achieve the objectives of 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	Order in TFLs
300 mg LOXO-305	1
600 mg LOXO-305	2
800 mg LOXO-305	3
900 mg LOXO-305	4

All treatments described above are the planned treatments. The TFLs will reflect the actual treatments received, and dose levels will be displayed in increasing order.

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 include all subjects who received one dose of 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 one 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}. The impact of protocol deviations on the PK population will be evaluated 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 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, changes from baseline, and any parameter derivations.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As ET data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.
- Postdose repeats and unscheduled assessments will not be included in calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.
- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 8.6.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

All protocol deviations and data issues (eg missing data, out of protocol window) that occur during the study, including those related to COVID-19, will be considered prior to database lock for their severity/impact on how the data will be displayed.

8.1.2. Repeat and Unscheduled Assessments

For vital sign measurements and 12-lead 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, clinical laboratory values), 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.

Postdose 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.

If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The mean change from baseline will be defined as the mean of the individual changes from baseline for all subjects.

See Section 8.1.2 for more detail on handling repeat and unscheduled readings in the calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment will be provided, based on the all subjects population.

8.3. Demographics and Baseline Characteristics

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

A summary table by treatment 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 dose of LOXO-305. Concomitant medication will be defined as medication that starts during or after dosing LOXO-305 or starts but does not end prior to dosing LOXO-305.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2020. Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of 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-inf}	h*ng/mL	area under the concentration-time curve from hour 0 extrapolated to infinity[c]
AUC_{0-24}	h*ng/mL	area under the concentration-time curve from hour 0 to 24 hours postdose
$\%AUC_{extrap}$	%	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 during the terminal phase
$DAUC_{0-t}$[d]	h*ng/mL/mg	AUC_{0-t} normalized by dose administered
$DAUC_{0-inf}$[d]	h*ng/mL/mg	AUC_{0-inf} normalized by dose administered
AUC_{0-24}[d]	h*ng/mL/mg	AUC_{0-24} normalized by dose administered
DC_{max}[d]	ng/mL/mg	C_{max} normalized by dose administered

[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
[d] Calculated by dividing the parameter by the dose (mg)

Additional PK parameters may be determined where appropriate.

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, $AUC_{0\text{-inf}}$, $t_{1/2}$, CL/F, and V_z/F) 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	1/h	apparent terminal elimination rate constant
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 area under the concentration-time curve (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}.

If the extrapolated area is >30%, $AUC_{0\text{-inf}}$ (and derived parameters) may be excluded from the summary statistics and statistical analysis at the discretion of the sponsor or pharmacokineticist.

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

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

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQs will be treated as missing. The following rules apply with special situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma concentration is missing, it may be set to zero 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 will be considered anomalous and set to missing for the PK analysis.

8.5.2. Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates from the nominal time by more than ±10%, the concentration will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For PK concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and coefficient of variation (CV) of geometric mean will be reported as not calculated (NC).

For PK parameters the following rule will apply:

- Geometric mean and coefficient of variation will not be calculated for t_{max}.

PK analysis will use actual times as recorded on the electronic case report form.

8.5.2.1. 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. 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 Analysis

A statistical analysis will be conducted to investigate the dose proportionality of $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}.

The natural log (ln) transformed LOXO-305 PK parameters will be analyzed using a power model[3, 4] that can be expressed as a linear regression equation with ln-transformed dose as a covariate:

$$ln(parameter) = intercept + slope \times ln(dose) + random\ error$$

For dose proportionality, the slope of the regression line is equal to 1; for dose independence, it is equal to 0.

At first, a statistical linear relationship between the ln-transformed PK parameters and the ln-transformed dose will be verified by including a quadratic (ln-transformed dose)^2 term in the model as indicated above. A 5% level of significance will be used for testing of the quadratic effect. If the quadratic term is not suggested from the model, the slope of ln(dose) around 1 suggests dose-proportionality from the linear regression model of ln-transformed PK parameters versus ln(dose).

For each PK parameter separately, an estimate of slope, corresponding 90% confidence interval (CI), and between-subject coefficient of variation (CV) will be calculated from the power model. Figures (on the logarithmic scale) containing individual values, power model line (90% CI), and dose proportionality line (defined as the power model line with slope of 1) will be created for each PK parameter; figures (on the semi-logarithmic scale) containing individual values and geometric means will be created for each corresponding PK parameter normalized by dose administered.

The lack of fit test will be conducted for the statistical assessment of linearity assumption, and thus appropriateness of a power model. The lack of fit model will be the same as the power model fitted, but with dose included as additional fixed effect. The statistical assessment will rule the linearity assumption acceptable if the diagnostic plots appear reasonable and the lack of fit p-value >0.05 (dose effect is not significant at the 0.05 level of significance). The assessment of linearity assumption may also occur via visual examination of the figures by the pharmacokineticist. This assessment may override the statistical assessment; where this occurs, it will be detailed in the CSR.

It will be concluded that PK parameter is dose proportional for the dose range studied if the assumption of linearity is ruled acceptable and the 90% CI for the slope spans 1.

If the assumption of linearity is ruled unacceptable for any PK parameter, its corresponding PK parameter normalized by dose administered will be ln-transformed and analyzed using an analysis of variance (ANOVA) model.[5] The model will include dose as a factor. For each PK parameter separately, the geometric least squares mean (GLSM) for each dose, p-values for the overall, and pairwise dose comparisons will be calculated.

Residual plots will be produced to assess the adequacy of the model(s) fitted.

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 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 LOXO-305 dosing, or starts prior to dosing and increases in severity after LOXO-305 dosing.

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 dosing 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
- 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 dosing.
- 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 dosing 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 evaluations, 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 timepoint.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ 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 $\leq x$ values will be set to 0, whereas $>x$ and $\geq x$ values will be set to x.

8.6.3. Vital Signs Results

All vital sign results with changes from baseline will be listed; any value outside the clinical reference range will be flagged, and whether the out of range value was deemed clinically significant or not clinically significant will be indicated.

The observed results and change from baseline for all vital signs results will be summarized descriptively by treatment and timepoint.

8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters with changes from baseline will be listed; any value outside the clinical reference range will be flagged, and whether the out of range value was deemed clinically significant or not clinically significant will be indicated.

The observed results and change from baseline for all 12-lead ECG parameters will be summarized descriptively by treatment and timepoint. QTcF values that are > 450 msec and increase from baseline > 30 msec will be flagged in the data listing.

8.6.5. Other Assessments

Medical history and physical examination will be listed. Any physical examination abnormalities reported will also be flagged as clinically significant or not clinically significant as indicated.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned.

10. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

Since the finalization of the protocol the dose levels of each cohort have been confirmed as 300 mg, 600 mg, 800 mg, and 900 mg, therefore these values have been included in Section 6 Study Treatments and within the TFL shells.

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. Gough K, Hutchinson M, Keene O, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/Pharmacokinetics UK Joint Working Party. *Drug Inf J*. 1995;29(3):1039-1048.

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

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

12. APPENDICES

Appendix 1: Document History

Status, Version	Date of Change	Summary/Reason for Changes
Final, Version 1.0	NA	NA; the first version.

NA = not applicable

Statistical Analysis Plan Approval Form

Sponsor Name:	Loxo Oncology, Inc.
Sponsor Protocol ID:	LOXO-BTK-20017
Covance Study ID:	8426665
SAP Text Filename:	LOXO-BTK-20017 SAP_SponsorFinal_V1.0.docx
TFL Shells Filename:	LOXO-BTK-20017 TFL Shells_SponsorFinal_V1.0.docx
Version:	Final 1
Date:	16 November 2020

Covance Approval(s):

PPD

16NOV2020
Date

16NOV 2020
Date

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study; and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based on this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

DocuSigned by:

PPD

17-Nov-20 | 09:06:53 PST
Date

Please scan/email completed form(s) to the Lead Statistician listed below:

Printed Name/Title:	PPD
Email:	