Statistical Analysis Plan J2N-OX-JZNT Version 1

A Phase I, Open-label, Fixed-sequence, Drug Interaction Study to Investigate the Effect of Single and Multiple Oral Doses of LOXO-305 on the Pharmacokinetics of Multiple Oral Doses of Digoxin (P-Glycoprotein Substrate) in Healthy Subjects

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

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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
Ae	amount excreted in urine per sampling interval
AUC_{0-24}	area under the concentration-time curve from hour 0 to 24 hours
AUC_{0-t}	area under the concentration-time curve from hour 0 to the last measurable concentration
AUC_{tau}	area under the concentration-time curve over a dosing interval
AR_{AUC}	accumulation ratio base on AUC_{tau}
BID	twice daily
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	maximum observed plasma concentration
CL/F	apparent systemic clearance
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CRU	Clinical Research Unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
Fe	percentage of dose excreted in urine per sampling interval
Geom CV	geometric CV
Geom Mean	geometric mean
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
λ_Z Lower	start of exponential fit
λ_Z N	number of data points included in the log-linear regression
λ_Z Span Ratio	time period over which λ_Z was determined as a ratio of $t_{1/2}$
λ_Z Upper	end of exponential fit

LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{last}	mean residence time based on AUC_{0-t}
NA	not applicable
NC	not calculated
NR	not reported
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
R^2-adj	adjusted coefficient for determination of exponential fit
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time to maximum observed plasma concentration
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 12 February 2021) and electronic case report form (eCRF).

This SAP describes the planned analysis of the pharmacokinetic (PK), 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. Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

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) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials*. [1,2,3]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of the study are:

- to assess the effect of single and multiple oral doses of LOXO-305 on the PK of multiple oral doses of digoxin (P-glycoprotein [P-gp] substrate) in healthy subjects.
- to assess the PK of LOXO-305 administered with multiple doses of digoxin at steady state in healthy subjects.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety and tolerability of single and multiple oral doses of LOXO-305 when coadministered with multiple oral doses of digoxin.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

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

- area under the concentration-time curve from hour 0 to the last measurable concentration (AUC_{0-t})
- area under the concentration-time curve over a dosing interval (AUC_{tau})
- apparent systemic clearance (CL/F)
- maximum observed plasma concentration (C_{max})
- time to maximum observed plasma concentration (t_{max})
- mean residence time based on AUC_{0-t} (MRT_{last})

The following PK parameters will be calculated whenever possible, based on the urine concentrations of digoxin:

- amount excreted in urine per sampling interval (Ae)
- percentage of dose excreted in urine per sampling interval (t_1-t_2), where $\%f_{eu} = 100$ (A_{eu}/dose)
- renal clearance (CL_r)

3.2. Secondary Endpoints

Safety and tolerability will be assessed by monitoring adverse events (AEs), performing physical examinations and clinical laboratory evaluations, measuring vital signs, recording 12-lead electrocardiograms (ECGs), and safety monitoring of serum digoxin levels.

4. STUDY DESIGN

This is a Phase 1, open-label, fixed-sequence drug-drug interaction study to investigate the effect of single and multiple oral doses of LOXO-305 on the PK of multiple oral doses of digoxin (P-gp substrate) in healthy subjects.

On Day 1, subjects will be administered oral 0.25 mg digoxin twice daily (BID) (loading dose), once in the morning and evening. Subjects will be fasted for at least 2 hours predose and 1-hour postdose for the morning and evening dose.

On Days 2 through 16, oral doses of 0.25 mg digoxin once daily (QD) will be administered (total of 17 consecutive doses) at the actual time of the Day 1 morning digoxin dose (± 1 hour). On Days 8 through 16 (9 consecutive doses), oral doses of

200 mg LOXO-305 QD will be coadministered with 0.25 mg digoxin QD, at the actual time of the Day 1 morning digoxin dose (± 1 hour). LOXO-305 will be administered first, immediately followed by digoxin. On Days 2, 4 through 6, 9 through 11, 13, and 14, subjects will fast for at least 2 hours predose and 1-hour postdose. On Days 3, 12, and 15 where clinical laboratory evaluations are performed, subjects will fast for at least 8 hours predose and 1-hour postdose. On Days 7, 8, and 16, subjects will be fasted at least 10 hours predose and 2 hours postdose. Blood and urine samples for concentrations of digoxin in plasma and urine and CCI [redacted]. Blood samples for concentrations of LOXO-305 and digoxin in plasma and CCI [redacted] Urine samples for concentrations of digoxin and CCI [redacted]

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 to receive a dose of study drug; this definition excludes screen failure subjects. Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects who are determined to be screen failures are permitted to be re-screened if the Investigator (or designee), with agreement from the Sponsor, feels that the subject may meet eligibility criteria upon re-screen. Re-screened subjects will be provided a new subject number.

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in).

Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 20 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Dosing of digoxin will occur on Days 1 through 16 and dosing of LOXO-305 will occur on Days 8 through 16. A follow-up phone call will occur for all subjects who received at least 1 dose of study drug (including subjects who are terminated early) 7 days (± 2 days) after EOT or ET. The duration of participation is expected to be approximately 58 days (Screening through 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, safety monitoring of serum digoxin levels, and recording of concomitant medications will be performed at specified times during the study.

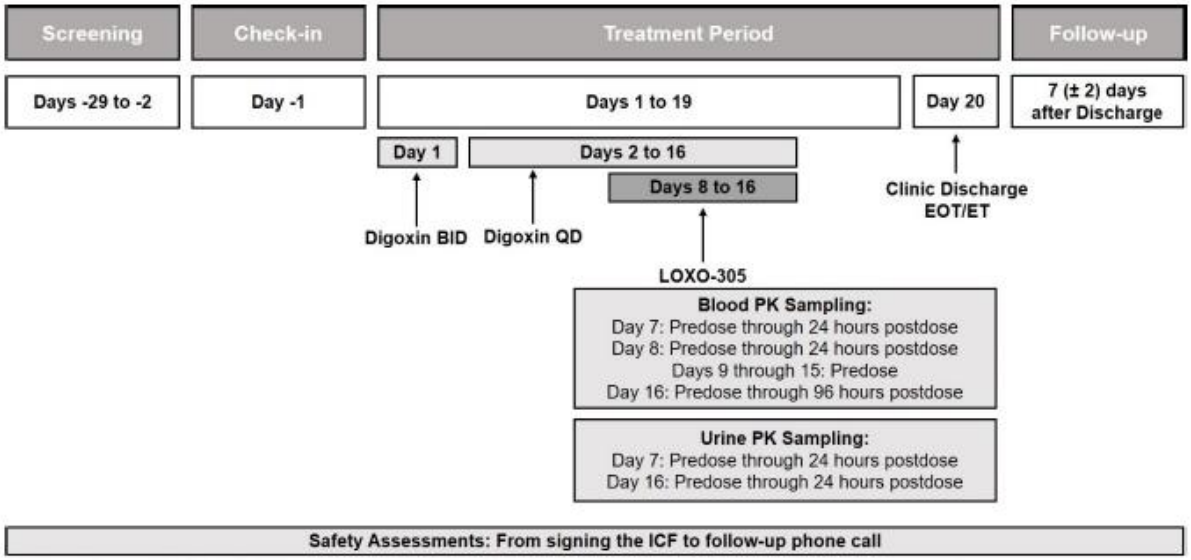
The AEs and serious adverse events (SAEs) will be collected beginning at informed consent. The AEs will be reported throughout the study (ie, from signing of the ICF until End of Study [EOS], or until ET if the subject discontinues from the study and does not complete a follow-up phone call), either 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.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



BID = Twice daily; QD = Once daily; EOT=End of treatment; ET= Early termination

5. SAMPLE SIZE JUSTIFICATION

Up to 16 healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. The sample size chosen for this study was selected without statistical considerations but is consistent with previous studies of a similar design. Up to 16 subjects are anticipated to be sufficient to provide a reliable estimate of the magnitude and variability of the interaction. Replacement subjects may be enrolled only if deemed necessary by the Sponsor. Every attempt will be made to enroll at least 4 subjects of each sex in the study.

6. STUDY TREATMENTS

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

Table 1: Presentation of Study Treatments in Safety TFLs

Study Treatment	Order in TFLs
0.25 mg Digoxin Alone	1
200 mg LOXO-305 QD + 0.25 mg digoxin QD	2

QD = once daily; TFL = table, figure, and listing.

All TFLs will be based on actual treatments.

Table 2 shows a list of the PK treatment labels and ordering that will be used in the TFLs.

Table 2: Pharmacokinetic Treatment Labels

Study Treatment Labels	Order in TFLs
0.25 mg Digoxin Alone	1
200 mg LOXO-305 Once + 0.25 mg digoxin QD	2
200 mg LOXO-305 QD + 0.25 mg digoxin QD	3

QD = once daily; TFL = table, figure, and listing.

The study treatment sequence names and ordering to be used in the TFLs are presented in Table 3.

Table 3. Presentation of Study Treatment Sequences in TFLs

Study Treatment Sequence	Order in TFLs
0.25 mg Digoxin BID (D1) / 0.25 mg Digoxin QD (D2-7) / 200 mg LOXO-305 QD + 0.25 mg digoxin QD (D8-D16)	1

BID = twice daily; QD = once daily; TFL = table, figure, and listing.

7. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those due to coronavirus disease 2019 (COVID-19) and related restrictions (see Section 8.1.1), 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 consist of all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The safety population will consist of all subjects who received at least 1 dose of study drug (digoxin and/or LOXO-305).

7.3. Pharmacokinetic Population

The PK population will consist of all subjects who received a dose of LOXO-305 or digoxin, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can

be computed. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times the median t_{max}. The impact of protocol deviations on the PK population will be evaluated on a case-by-case basis.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they completed all protocol-specified procedures and assessments for the EOS visit. Any subject who discontinues 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 a new version is issued 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 a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.2 (or higher if a new version is issued during the study). Pinnacle 21 Community Validator Version 3.1.0 (or higher if a new version is issued during the study) will be utilized to ensure compliance with CDISC standards.

For all statistical analyses, the hypothesis testing will be 2-sided and carried out on 0.05 significance level, unless specifically stated otherwise.

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 ‘valid’ data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to ‘all calculations’, this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation and changes from baseline.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

8.1.1. Handling of Data Quality Issues Due to Coronavirus Disease 2019 and Related Restrictions

Due to COVID-19 and related restrictions, there is a high risk for impact to data integrity, with the recognized potential for:

- Missed visits, caused by, for example:

  - Subject unable to travel to site due to restrictions, the need to quarantine, or COVID-19 infection
  - Subject unwilling to go to site due to fear of COVID-19 infection
  - Site postponing subject's visit due to investigator not being available (eg, if they have been dispatched to hospital handling COVID-19 infections)

- Site unable to replenish supply of investigational product
- Incomplete data entry by sites due to limited resources to support study or no access to source documents or to eCRF
- Outstanding source document verification (SDV) due to sponsor or country restrictions on remote SDV, or no or limited access to site(s) for on-site visits
- Unanswered queries

At the time of the reporting of the study results, all protocol deviations due to COVID-19 or related restriction will be assessed for their severity and impact on the analyses. If needed, appropriate statistical methods will be applied as a mitigating action (eg, data might be categorized into 2 analysis groups, with and without COVID-19 and related restrictions impact); however, this will exclude any imputations of the missing values. Any mitigating actions will be agreed with Loxo Oncology, Inc. in advance and identified in the CSR.

8.1.2. 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.
- In general, as ET data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics and statistical analyses. Exceptions may be made where justified.
- Postdose repeats and unscheduled assessments will not be included in calculations of summary statistics.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.

- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 subject represented will be included; unless specifically stated otherwise.

- Missing values will not be imputed, 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.

8.1.3. Repeat and Unscheduled Readings

For vital signs 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, 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.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 8.1.4).

8.1.4. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last non-missing measurement before administration of study drug on Day 1. 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 first dose.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the postdose timepoint.

The summary statistics for change from baseline will be derived from individual subjects' values (eg, mean change from baseline will be the mean of the individual changes from baseline for all subjects, rather than difference between the mean value at the postdose timepoint and mean value at baseline).

See Section 8.1.3 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 safety population.

8.3. Screening Demographics

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

A summary table by treatment sequence will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to the first dose. Concomitant medication will be defined as medication that starts during or after the first dose or starts but does not end prior to the first dose.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version September 2020 (or later if a new version is issued during the study; see the data management plan [DMP] for more details). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following plasma PK parameters will be determined where possible from the plasma concentrations of LOXO-305 and digoxin 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_{tau}	h*ng/mL	area under the concentration-time curve over a dosing interval[b] (tau=24 hours)
C_{max}	ng/mL	maximum observed plasma concentration
t_{max}	H	time to maximum observed plasma concentration
CL/F	L/h	apparent systemic clearance
MRT_{last}	H	mean residence time (based on AUC_{0-t})
AR_{AUC}	NA	accumulation ratio base on AUC_{tau} (LOXO-305 only)

NA Not applicable
[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

For each subject, the following urine PK parameters will be calculated, whenever possible, based on the urine concentrations of digoxin:

Parameter	Units[a]	Definition
Ae	mg	amount excreted in urine per sampling interval (t1-t2)
CL_R	L/h	renal clearance

%feu	%	percentage of dose excreted in urine per sampling interval (t1-t2), where [redacted]

[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.

Additional PK parameters may be determined where appropriate, e.g. terminal elimination half-life ($t_{1/2}$) after last dose (Day 16) with sample collections up to 96 hours postdose.

The PK analysis will be carried out where possible using actual blood sampling times postdose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max} and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

8.5.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The following will be reported only if $t_{1/2}$ is calculable. The start of the terminal elimination phase for each subject will be defined by the pharmacokinetic software and confirmed 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) and its associated half-life ($t_{1/2}$) 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.

The following regression-related diagnostic PK parameters will be determined, when possible:

Parameter	Units	Definition
λ_z Upper	H	end of exponential fit
λ_z Lower	H	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_Z was determined as a ratio of $t_{1/2}$
R^2-adj	NA	adjusted coefficient for determination of exponential fit

NA = Not applicable.

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥ 2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

8.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

8.5.1.3. Calculation of Urinary Parameters

The amount of the dose administered recovered (Ae) in urine for digoxin urine collection interval (t_1-t_2) will be calculated as the product of urine concentration and urine volume. CCI [redacted] A total cumulative $Ae_{0\text{-}x\ h}$ will be calculated by summing the $Ae_{t1\text{-}t2}$ values over the 0-x h interval, where x = end of the last collection time interval.

The percentage of the administered dose for digoxin recovered over the time interval t1 to t2 ($Fe_{t1\text{-}t2}$) will be calculated for each urine collection interval as follows:

CCI [redacted]

Cumulative $fe_{0\text{-}x\ h}$ will be calculated by summing the $fe_{t1\text{-}t2}$ values over the 0-x h period in the same manner as $Ae_{0\text{-}x\ h}$.

Renal clearance (CL_R) will be calculated over 0-t according to the following formula, where cumulative Ae and AUC are calculable to the same end time (t):

CCI [redacted]

8.5.1.4. 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 the concentration value at 24 hours postdose after repeated QD doses.

Urine concentrations that are BLQ will be set to 0 for the calculation of $Ae_{t1\text{-}t2}$.

8.5.1.5. 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

All PK concentrations and parameters will be listed.

Summary tables, arithmetic 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-linear and linear-logarithmic scales, with the exception of figures across all days, which will be produced on the linear-linear scale only. The +SD bars will only be displayed on the linear-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 and urine 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.

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}.

Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For plasma 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).

Urine concentration data will be listed only.

For PK parameters the following rule will apply:

- For the calculation of summary statistics of PK parameters, all not reported (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}.

- Geometric mean and CV will not be calculated for t_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

A statistical analysis will be conducted to investigate the drug-drug interaction on the PK of the following comparisons:

Plasma PK only

- Multiple doses of digoxin coadministered with a single dose of LOXO-305 versus multiple doses of digoxin alone.

Plasma and urine PK

- Multiple doses of digoxin coadministered with multiple doses of LOXO-305 versus multiple doses of digoxin alone.

The natural log-transformed[4] PK parameters (AUC_{0-t}, AUC_{tau}, C_{max},$Ae_{0-x\ h}$ and CL_R) will be analyzed using a mixed effect model.[5] The model will include actual treatment as a fixed effect, and subject as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% confidence interval (CI) will be calculated; these values will then be exponentiated to give the geometric least squares mean, geometric mean ratios, and corresponding 90% CI.

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

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

Mixed Model Analysis

```
proc mixed data = <data in>;
  by parcat1n parcat1 pkday paramn param;
  class trtan usubjid;
  model lpk = trtan / cl residual ddfm = kr2;
  lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
  random intercept / subject = usubjid;
  ods output lsmeans = <data out>;
  ods output diffs = <data out>;
  ods output covparms = <data out>;
```

```
run;
```

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 (or higher if a new version is issued during the study). All AEs will be assigned a severity grade using National Cancer Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (or higher if a new version is issued during the study).

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 and digoxin), as determined by the investigator.

The assignment of TEAEs to treatments will be as follows:

- A TEAE occurring during or after Day 1 dosing will be assigned to 0.25 mg digoxin alone.
- A TEAE occurring during or after Day 8 dosing of LOXO-305 will be assigned to 200 mg LOXO-305 QD + 0.25 mg digoxin QD.

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 associated dose for TEAEs only. Where the last associated dose is referring to the last dose received prior to the start of a TEAE.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the first dose.

- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.

- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of the last dose is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters and their 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.

Summary tables by treatment and timepoint will be provided for clinical chemistry, hematology, and coagulation parameters, and their changes from baseline, as applicable.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, <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 and their changes from baseline will be listed, as applicable; 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.

Summary tables by treatment and timepoint will be provided for all vital signs parameters and their changes from baseline, as applicable.

8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters and their 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.

Summary tables by treatment and timepoint will be provided for all 12-lead ECG parameters, along with their changes from baseline.

QT interval corrected for heart rate using Fridericia's formula (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, physical examination and digoxin concentrations will be listed. Any physical examination abnormalities reported and abnormal digoxin concentrations will also be flagged as clinically significant or not clinically significant as indicated.

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

8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

The primary endpoint "area under the concentration-time curve from hour 0 to 24 hours (AUC0-24)" has been removed as this is a repeat of the following primary endpoint "area under the concentration-time curve over a dosing interval (AUC_{tau})" since for this study tau is equal to 24 hours.

11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

2. ICH. ICH Harmonised Tripartite Guideline: General considerations for clinical trials (E8). 17 July 1997.

3. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

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

NA = not applicable

Statistical Analysis Plan (SAP)/Initiation of Programming Approval Form

Type of Approval (select one) : ☒ **SAP** ☐ **Initiation of Programming**

Sponsor Name:	Loxo Oncology, Inc.
Sponsor Protocol ID:	LOXO-BTK-20021
Covance Study ID:	8456071
SAP Text Filename:	LOXO-BTK-20021_SAP_Sponsor_Final_V1.0.docx
TFL Shells Filename:	LOXO-BTK-20021_TFL Shells_Sponsor_Final_V1.0.docx
Version:	Final 1.0
Date:	20 May 2021

Covance Approval(s):

Lead Statistician

Approval Signature Print Name Job Title Date	PPD 20MAY2021

Lead Pharmacokineticist

Approval Signature Print Name Job Title Date	PPD 20 may 2021

Sponsor Approval:

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 Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Approval Signature Print Name Job Title Date	PPD 23-May-21 | 00:56:09 EDT PPD Signing Reason: I approve this document Signing Time: 23-May-21 | 00:56:02 EDT 50FB5B25121D47D8BA1D114FE51F3864

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

Printed Name/Title:	PPD
Email:	