Statistical Analysis Plan LOXO-BTK-20016

A Phase I, Open-label, Fixed-sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of Pirtobrutinib (LOXO-305) on the Pharmacokinetics of Repaglinide (CYP2C8 Substrate) in Healthy Subjects

NCT06165146

Approval date: 18-Dec-2020

Statistical Analysis Plan

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SAP Status: Sponsor Final
SAP Version: 1.0
SAP Date: 18DEC2020

Investigational Product: LOXO-305

Protocol Reference: LOXO-BTK-20016
Covance Study: 8425120

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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
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	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
CL_{ss}/F	apparent systemic clearance at steady state
C_{max}	maximum observed concentration
COVID-19	SARS-CoV-2
C_{trough}	concentration observed at the end of the dosing interval
CRU	Clinical Research Unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
ET	early termination
Geom CV	Geometric CV
Geom Mean	Geometric mean
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
λ_Z	apparent terminal elimination rate constant
ln	natural log
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated

PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time to maximum observed 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 05 October 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 Objective

The primary objective of the study is:

- to assess the impact of multiple oral doses of LOXO-305 on the PK of a single oral dose of repaglinide (CYP2C8 substrate) in healthy subjects.

2.2. Secondary Objective

The secondary objective of the study is:

- to assess the safety and tolerability of multiple oral doses of LOXO-305 when administered alone and coadministered with repaglinide in healthy subjects.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The following PK parameters will be calculated, whenever possible, based on the plasma concentrations of repaglinide following single oral dose administration (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 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 concentration (t_{max})
- apparent terminal elimination rate constant (λ_Z)
- apparent systemic clearance (CL/F)
- apparent terminal elimination half-life ($t_{1/2}$)
- apparent volume of distribution (V_z/F).

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

- AUC_{0-t}
- AUC during a dosing interval (AUC_{tau})
- C_{max}
- concentration observed at the end of the dosing interval (C_{trough})
- t_{max}
- CL/F at steady state (CL_{ss}/F).

3.2. Secondary Endpoints

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.

4. STUDY DESIGN

This is a Phase 1, open-label, 2-period, fixed-sequence drug-drug interaction study to investigate the effect of multiple oral doses of LOXO-305 on the PK of a single oral dose of repaglinide in healthy subjects.

In Period 1, Day 1, a single 0.5 mg oral dose of repaglinide will be administered in the morning, following a fast of at least 10 hours prior to dosing. In order to mitigate any side effects when dosing with repaglinide on Day 1, on Day -1, subjects will be offered breakfast, lunch, dinner, and an optional snack after dinner. On Day 1, subjects will receive a

standardized light breakfast 15 minutes postdose. In addition, subjects may be provided with up to 16 g of glucose (up to 4 x 4 g chewable tablets) approximately 1-hour post-dose , if needed. Glucose values may be checked for subjects suspected of having low blood sugar or being hypoglycemic by fingerstick glucose tests prior to and/or following administration of glucose tablets at the discretion of the PI (or designee). Blood samples for concentrations of repaglinide in plasma will be collected CCI .

In Period 2, on Days 2 through 11, oral doses of 200 mg LOXO-305 will be administered QD in the morning at the actual time of the Day 1 repaglinide dose (± 1 hour). On Days 2 through 11, subjects will fast for at least 2 hours predose and 1-hour postdose with the exception of Days 2, 6, and 11 where clinical laboratory evaluations are performed, subjects will fast for at least 8 hours predose and 1-hour postdose. On Day 12, 200 mg LOXO-305 and 0.5 mg of repaglinide will be co-administered in the morning at the actual time of the Day 1 repaglinide dose (± 1 hour), following a fast of at least 10 hours prior to dosing. In order to mitigate any side effects when dosing with repaglinide on Day 12, on Day 11, subjects will receive breakfast (2 hours after dosing), lunch, dinner, and an optional snack after dinner. On Day 12, subjects will receive a standardized light breakfast 15 minutes post-LOXO-305 and repaglinide dosing. In addition, subjects may be provided with up to 16 g of glucose (up to 4 x 4 g chewable tablets) approximately 1-hour post-LOXO-305 and repaglinide dosing, if needed. Glucose values may be checked for subjects suspected of having low blood sugar or being hypoglycemic by fingerstick glucose tests prior to and/or following administration of glucose tablets at the discretion of the PI (or designee).

On CCI a CCI CCI . CCI , blood samples for concentrations of repaglinide and LOXO-305 in plasma will be collected CCI

There will be a washout period of 11 days between the dose of repaglinide on Day 1 and the dose of repaglinide on Day 12, respectively.

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 16 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 (± 2 days) after EOT or ET. The duration of participation is expected to be approximately 54 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.

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 adverse events (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.

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

5. SAMPLE SIZE JUSTIFICATION

Up to CCI [redacted] 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 CCI [redacted] 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 sequence name and ordering to be used in the TFLs are presented in Table 1.

Table 1: Presentation of Study Treatment Sequence in TFLs

Study Treatment Sequence	Order in TFLs
0.5 mg repaglinide alone/200 mg LOXO-305 QD alone/200 mg LOXO-305 QD + 0.5 mg repaglinide	1

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

Table 2: Presentation of Study Treatments in TFLs

Study Treatment	Order in TFLs (PK)	Order in TFLs (all others)
0.5 mg repaglinide alone	1	1
200 mg LOXO-305 QD alone	3	2
200 mg LOXO-305 QD + 0.5 mg repaglinide	2	3

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

7. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those related to SARS-CoV-2 (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 at least 1 dose of study drug (repaglinide and/or 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 a dose of LOXO-305, have at least 1 quantifiable plasma concentration, and for whom at least 1 PK parameter can be computed. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median t_{max} for the analyte being evaluated. The impact of protocol deviations on PK population will be evaluated on a case-by-case basis.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they completed all protocol-specified procedures and assessments for the EOT visit. Any subject who discontinued the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.2 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 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.
- 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.

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

8.1.2. Repeat and Unscheduled Readings

For vital sign measurements and 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 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 post dose. In the event of any repeats or unscheduled measurements taken pre-dose the values will be considered when determining the baseline value.

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 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 dosing of study drug.

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

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

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of LOXO-305 and repaglinide using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Repaglinide; following a single dose of repaglinide alone (Day 1) and in combination with multiple doses of LOXO-305 (Day 12)

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]
$\%AUC_{extrap}$	%	percentage extrapolation for AUC_{0-inf}
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time to maximum observed 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

[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

LOXO-305; following daily multiple doses of LOXO-305 and a single dose of repaglinide (Day 12)

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 during a dosing interval
C_{max}	ng/mL	maximum observed concentration

C_{trough}	ng/mL	concentration observed at the end of the dosing interval
t_{max}	h	time of the maximum observed concentration
CL_{ss}/F	L/h	apparent systemic clearance at steady state

[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.

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 for $AUC_{0\text{-}inf}$ is >30%, $AUC_{0\text{-}inf}$ (and derived parameters) will 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 time point or $AUC_{0\text{-}t}$, may be used in the statistical analysis.

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

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

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a Day 1 or Day 12 predose repaglinide plasma concentration is missing, it may be set to zero by default. If a Day 12 predose concentration of LOXO-305 is missing, the concentration at 24 hours may be used as the predose value.

8.5.1.4. Treatment of Outliers in Pharmacokinetic Analysis

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

Any quantifiable predose concentration value for repaglinide on Days 1 or 12 will be considered anomalous and set to missing for the PK analysis.

8.5.2. Presentation of Pharmacokinetic Data

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

For PK concentration data the following rules will apply:

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

For PK parameters the following rule will apply:

- Geom Mean and CV will not be calculated for t_{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, 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, Geom Mean and geometric CV [Geom CV]) will be calculated for plasma LOXO-305 and repaglinide 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.

8.5.3.1. Statistical Analysis

A statistical analysis will be conducted to investigate the drug-drug interaction of LOXO-305 on repaglinide for AUC_{0-t}, AUC_{0-inf}, and C_{max}. The comparisons of interest are:

To assess the impact of multiple oral doses of LOXO-305 on the single dose PK of repaglinide (AUC_{0-t}, AUC_{0-inf}, and C_{max})

- 200 mg LOXO-305 co-administered with 0.5 mg repaglinide (Day 12) (test treatment) vs 0.5 mg repaglinide (Day 1) (reference treatment).

The natural log (ln) transformed PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) will be analyzed using a mixed model[3]. The model will include actual treatment as 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.

Mixed Model Analysis

```
proc mixed data = <data in>;

  class treatment usubjid;
  model lpk = treatment / cl residual ddfm = kr;
  lsmeans treatment / 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 23.1. 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 repaglinide, or starts prior to the first dose and increases in severity after the first dose.

A treatment-related TEAE will be defined as a TEAE with a relationship of related to the study treatment, as determined by the investigator.

If deemed related to study treatment, the assignment of TEAEs to treatments will be as follows:

- A TEAE occurring during or after Day 1 dosing and prior to Day 2 dosing will be assigned to 0.5 mg repaglinide
- A TEAE occurring during or after Day 2 dosing and prior to Day 12 dosing will be assigned to 200 mg LOXO-305
- A TEAE occurring during or after Day 12 dosing will be assigned to 200 mg LOXO-305 + 0.5 mg repaglinide

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the last dose for TEAEs only.

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

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

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

The frequency of subjects with TEAEs will be summarized separately for all 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 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.

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, ≤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 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. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

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

11. REFERENCES

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

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

3. 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