Statistical Analysis Plan LOXO-BTK-21050 (J2N-OX-JZNV) Version 1.0

A Phase I, Open-Label, Randomized, 2-Way Crossover Study to Compare the PK of Pirtobrutinib (LOXO-305) Tablets

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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]).

$\%AUC_{extrap}$	percentage of $AUC_{0\text{-}inf}$ due to extrapolation from the last quantifiable concentration to infinity
ADaM	Analysis Data Model
AE	adverse event
$AUC_{0\text{-}t}$	area under the concentration-time curve from hour 0 to the time of the last quantifiable concentration
$AUC_{0\text{-}24}$	area under the concentration-time curve from hour 0 to 24 hours postdose
$AUC_{0\text{-}inf}$	area under the concentration-time curve from hour 0 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 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
Geom CV	geometric CV
Geom Mean	geometric mean
GLSM	geometric least square mean
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
λ_z	apparent terminal elimination rate constant
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
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{inf}	mean residence time based on $AUC_{0\text{-}inf}$
NA	Not applicable
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	reference
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
T	test
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of the maximum observed concentration
V_z/F	apparent volume of distribution during the 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 31 August 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 first subject enrollment (the point of enrollment occurs at the time of subject number allocation). 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*, and 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 Objective

The primary objective of the study is to assess the relative bioavailability of a pirtobrutinib tablet lot with a slower dissolution profile (T) relative to the pirtobrutinib tablet lot currently used in the clinical setting (R) following single doses of pirtobrutinib, as assessed by pirtobrutinib PK in healthy adult subjects.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety and tolerability of single doses of pirtobrutinib when administered as a test tablet lot and a reference tablet lot in healthy adult subjects.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The following PK parameters will be calculated, whenever possible, based on the plasma concentrations of pirtobrutinib (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 time of the last quantifiable concentration (AUC_{0-t})
- Area under the concentration-time curve from hour 0 extrapolated to infinity (AUC_{0-inf})
- Percentage of AUC_{0-inf} due to extrapolation from the last quantifiable concentration to infinity ($\%AUC_{extrap}$)
- Apparent systemic clearance (CL/F)
- Apparent terminal elimination half-life ($t_{1/2}$)
- Maximum observed concentration (C_{max})
- Time of the maximum observed concentration (t_{max})
- Apparent terminal elimination rate constant (λ_z)
- Apparent volume of distribution during the terminal phase (V_z/F)

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, and recording 12-lead electrocardiograms (ECGs).

4. STUDY DESIGN

This is a Phase 1, open-label, randomized, 2-way crossover study to compare the PK of 2 different lots of pirtobrutinib after a single oral dose in healthy adult subjects.

A single oral dose of pirtobrutinib will be administered as test lot tablets (T2-L [T]) or reference lot tablets (T2-PR [R]). The 2 treatment sequences will be TR and RT. Subjects will be randomly assigned to 1 of the 2 treatment sequences, according to a randomization scheme issued by Labcorp Drug Development. Up to 28 healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. Replacement subjects may be enrolled only if deemed necessary by the Sponsor. Every attempt will be made to enroll at least 3 subjects of each sex in the study.

In Treatment T, a single oral dose of 200 mg pirtobrutinib (2 × 100 mg) as test lot tablets will be administered in the morning on Day 1 or Day 8 (according to the randomization scheme), following a fast of at least 10 hours prior to and 4 hours after dosing. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose administration.

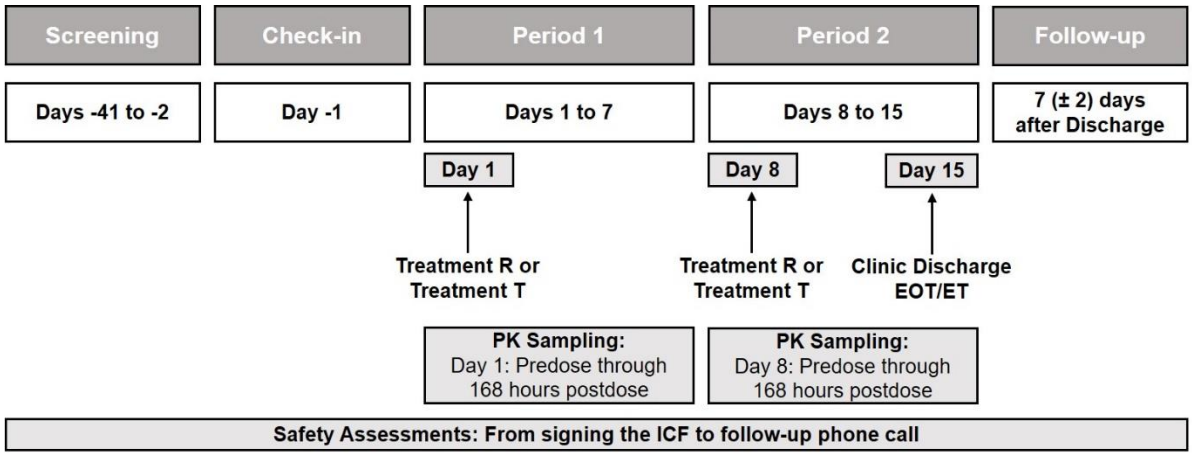
In Treatment R, a single oral dose of 200 mg pirtobrutinib (2 × 100 mg) as reference lot tablets will be administered in the morning on Day 1 or Day 8 (according to the randomization scheme), following a fast of at least 10 hours prior to and 4 hours after dosing. Water will be restricted for 1 hour prior to and 1 hour after dosing with the exception of water administered for dose administration.

Blood samples for the analysis of plasma concentrations of pirtobrutinib and for future potential and/or exploratory analysis will be collected from predose through 168 hours postdose for Treatment R and Treatment T.

There will be a washout period of 7 days between the doses of pirtobrutinib administered in Treatments R and T.

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

Figure 1: Study Design



Abbreviations: EOT = End of Treatment; ET = Early Termination; ICF = Informed Consent Form; PK = pharmacokinetic.

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. A minimum of 7 days must elapse between date of screen failure and date of re-screening.

To assess their eligibility to enter the study, potential subjects will be screened within 40 days (Days -41 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 15 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Subjects will be dosed on Day 1 and Day 8. 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 65 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, and recording of concomitant medications will be performed at specified times during the study.

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

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

5. SAMPLE SIZE JUSTIFICATION

Up to 28 healthy adult male and female subjects (women of non-childbearing potential only) will be enrolled. This is a relative bioavailability study; however, a total of 28 evaluable subjects (14 subjects per treatment sequence) will provide at least CCI power to have the respective 90% confidence intervals (CIs) for the geometric mean ratios for C_{max} and AUC values between test and reference lot tablets are within the interval of 80.00% to 125.00%, assuming a CCI and that the expected ratio of means is 1.05 (or 0.95). Based on PK results of LOXO-BTK-20009, CCI Replacement subjects may be enrolled only if deemed necessary by the Sponsor. Every attempt will be made to enroll at least 3 subjects of each sex in the study.

6. STUDY TREATMENTS

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

Table 1: Presentation of Study Treatments in TFLs

Study Treatment	Abbreviation	Order in TFLs
200 mg pirtobrutinib reference lot tablets	R	1
200 mg pirtobrutinib test lot tablets	T	2

All TFLs will be based on actual treatments (eg, if subject was assigned to receive reference but was wrongfully dosed with test treatment they would be summarized and listed under test treatment).

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

Table 2: Presentation of Study Treatment Sequences in TFLs

Study Treatment Sequence	Abbreviation	Order in TFLs
200 mg pirtobrutinib reference lot tablets / 200 mg pirtobrutinib test lot tablets	R/T	1
200 mg pirtobrutinib test lot tablets / 200 mg pirtobrutinib reference lot tablets	T/R	2

The summaries will be based on planned treatment sequences and listings will be based on actual treatment sequences (eg, if subject was assigned to receive reference in Period 1 and test treatment in Period 2 (sequence 'R/T') but was wrongfully dosed with test treatment in Period 1 and discontinued before start of Period 2, they would be summarized under 'R/T' treatment sequence and listed under 'T' treatment sequence).

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 include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment (pirtobrutinib). 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 study treatment (pirtobrutinib), have at least 1 quantifiable plasma concentration, and for whom at least 1 PK

parameter can be computed. 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 complete the scheduled EOS phone call (rather than ET 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 2.2.0 (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.

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.

Any protocol deviations and data issues (eg missing data, out of protocol window) that occur during the study, including those due to COVID-19 and related restrictions (see Section 8.1.1), will be considered prior to database lock for their severity and impact on the analyses.

8.1.1. Handling of Data Quality Issues Such as Missing Data and Protocol Deviations 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.

Any protocol deviations and data issues (eg missing data, out of protocol window) that occur during the study, including those due to COVID-19 and related restrictions (see Section 8.1.1), will be considered prior to database lock 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 early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics. 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 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). Post dose repeats and ET measurements will also 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 value recorded prior to dosing in each period. In general, baseline will be the predose value collected on Day 1 for period 1 and on Day 8 for period 2, respectively. For clinical chemistry, baseline for period 2 will be the value collected on Day 7 in period 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 in each period.

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 and Baseline Characteristics

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

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

8.4. Prior and Concomitant Medication

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

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version September 2021 (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 PK parameters will be determined where possible from the plasma concentrations of pirtobrutinib 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 time of the last quantifiable concentration (t_{last})[b]
AUC_{0-24}	h*ng/mL	area under the concentration-time curve from hour 0 to 24 hours postdose
AUC_{0-inf}	h*ng/mL	area under the concentration-time curve from hour 0 extrapolated to infinity[c]
$\%AUC_{extrap}$	%	percentage of AUC_{0-inf} due to extrapolation from the last quantifiable concentration to infinity
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time of the maximum observed concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent systemic clearance
MRT_{inf}	h	mean residence time (based on AUC_{0-inf})
V_z/F	L	apparent volume of distribution during the terminal phase

[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] The AUC will be calculated using the linear trapezoidal rule for increasing and decreasing concentrations.
[c] Based on the last observed quantifiable concentration.

Additional PK parameters may be determined where appropriate.

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 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 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}.

The $AUC_{0\text{-inf}}$ values where the percentage extrapolation is less than 30% will be reported. The $AUC_{0\text{-inf}}$ values where the percentage extrapolation is greater than 30% will be listed but excluded from descriptive statistics.

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 comparison of treatments.

8.5.1.3. Criteria for Handling Concentration 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 BLQ concentrations will be treated as missing. The following rules apply to the specific 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 will be set to 0 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 in the first treatment period will be considered anomalous and set to missing for the PK analysis. A missing predose concentration will be set to 0 by default in Phoenix WinNonlin.

If the predose concentration is >5% of C_{max} in the second treatment period, all PK concentration and parameter data will be excluded from the summary statistics and statistical analysis for that period.

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 by treatment, and individual figures with treatments overlaid will be provided for plasma PK concentrations. All figures will be produced on both linear-linear and linear-logarithmic scales. 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 pirtobrutinib PK parameters. Individual values and geometric means of PK parameters will be plotted.

A subject may be excluded from the PK summary statistics and statistical analysis when the subject has an AE of vomiting that occurs on 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 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 CV of geometric mean will be reported as not calculated.

For PK parameters the following rule will apply:

- 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 relative bioavailability of 200 mg pirtobrutinib test lot tablets (test treatment) versus 200 mg pirtobrutinib reference lot tablets (reference treatment).

The hypothesis testing will be 2-sided and carried out on 0.1 significance level.

The natural log (ln)-transformed[4] AUC_{0-t}, AUC_{0-inf}, and C_{max} (only for plasma pirtobrutinib) will be analyzed using a mixed model.[5] The model will include planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% CI will be calculated; these values will then be back-transformed to give the geometric least square mean (GLSM), geometric mean ratio (GMR), and corresponding 90% CI.

It will be concluded that the test treatment is bioequivalent to the reference treatment if, for all tested PK parameters, the 90% CI for GMR is completely contained within the predefined interval of (80.00%, 125.00%).[6] This procedure is equivalent to Schuirmann's[7] two one-sided tests at the 0.05 level of significance.

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

Examples 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 aperiod trtseqp usubjid;
  model lpk = trtan aperiod trtseqp / cl residual ddfm = kr;
  lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
  random intercept / subject = usubjid(trtseqp);
  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 24.1 (or higher if a new version is issued during the study; see the DMP for more details). All AEs will be assigned a severity grade using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (or higher if a new version is issued during the study; see the protocol for more details).

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, 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 the last associated 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 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 treatment-emergent status (applicable to all AEs): 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 status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, that TEAE will be counted under the 'missing' category.

- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE 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 associated dose is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE 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). If the start date of a TEAE is the same as the date of the last associated dose but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.

- For the derivation of duration (applicable to all AEs): 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 an 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). Any clock changes will be accounted for in the derivation.

- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.

- For the calculation of TEAE 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, 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. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

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, and presentation in the figures, <x, ≤x, >x and ≥x values will be set to x i.e. will be considered equal to the lower or upper limit of quantification, respectively.

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 oxygen saturation, respiratory rate, oral body temperature, systolic blood pressure, diastolic blood pressure, and pulse rate, and their changes from baseline, as applicable.

8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters 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. 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 and physical examination will be listed. Medical history will not be coded per MedDRA, and will be presented as reported (verbatim) on the eCRFs. 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: 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.

6. *Statistical Approaches to Establishing Bioequivalence*. Rockville, MD: US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); January 2001.

7. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm*. 1987;15(6):657-680.

12. APPENDICES

Appendix 1: Document History

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

NA = not applicable