Statistical Analysis Plan J2N-OX-JZNG Version 1.0

An Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-305 Administered to Fasted Renally Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

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Sponsor:
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Study Site:
Multiple Sites

Principal Investigator:
Multiple Investigators

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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 extrapolation for area under the concentration-time curve extrapolated to infinity
ADaM	analysis data model
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from hour 0 extrapolated to infinity
$AUC_{0\text{-}inf,u}$	unbound area under the concentration-time curve from hour 0 extrapolated to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from hour 0 to the last measurable concentration
$AUC_{0\text{-}t,u}$	unbound area under the concentration-time curve from hour 0 to the last measurable concentration
BLQ	below the limit of quantification
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
CL/F	apparent systemic clearance
$CL/F_{,u}$	unbound apparent systemic clearance
C_{max}	maximum observed plasma concentration
$C_{max,u}$	unbound maximum observed plasma concentration
CRU	Clinical Research Unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
f_u	unbound fraction
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
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 area under the concentration-time curve from time 0 extrapolated to infinity
NC	not calculated
NR	not reported
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
R^2-adj	adjusted coefficient for determination of exponential fit
COVID-19	SARS-CoV-2
SAE	serious adverse event(s)
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	apparent plasma terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time to maximum observed plasma concentration
V_z/F	apparent volume of distribution at the terminal phase
$V_z/F_{,u}$	unbound apparent volume of distribution at 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 2.0 dated 17 February 2021) 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 evaluate the PK profile of LOXO-305 in subjects with impaired renal function compared to matched-control healthy subjects.

2.2. Secondary Objective

The secondary objective of the study is to evaluate safety and tolerability of LOXO-305 in subjects with impaired renal function and matched-control healthy subjects.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of LOXO-305:

- maximum observed plasma concentration (C_{max})
- time to maximum observed plasma concentration (t_{max})

- area under the concentration-time curve (AUC) 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} ($\%AUC_{extrap}$)
- apparent terminal elimination rate constant (λ_z)
- apparent plasma terminal elimination half-life ($t_{1/2}$)
- apparent systemic clearance (CL/F)
- apparent volume of distribution at the terminal phase (V_z/F)
- mean residence time based on AUC_{0-inf} (MRT_{inf}).

In addition, a single blood sample will be collected predose to determine the unbound fraction (f_u) of LOXO-305 in plasma and, whenever possible, the following PK parameters will be calculated for unbound LOXO-305 using f_u: unbound C_{max} ($C_{max,u}$), unbound AUC_{0-t} ($AUC_{0-t,u}$), unbound AUC_{0-inf} ($AUC_{0-inf,u}$), unbound CL/F ($CL/F_{,u}$), and unbound V_z/F ($V_z/F_{,u}$).

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 electrocardiogram (ECGs). These safety and tolerability endpoints are deemed adequate to detect any safety signals.

4. STUDY DESIGN

This study is an open-label, nonrandomized, multi-center, single-dose, parallel-group study to determine the PK, safety, and tolerability of LOXO-305 administered orally at a dose of 200 mg to fasted adult males and females with impaired renal function and healthy subjects with normal renal function. Renal function will be classified based on the baseline estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation outlined in Table 1.

Table 1: The CKD-EPI Equation[3] to be used for eGFR Estimation

Sex and race	Serum creatinine (mg/dL)	Equation
Female Black	≤ 0.7	$eGRF = 166 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
	> 0.7	$eGRF = 166 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
Male Black	≤ 0.9	$eGRF = 163 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
	> 0.9	$eGRF = 163 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$
Female White or other	≤ 0.7	$eGRF = 144 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
	> 0.7	$eGRF = 144 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤ 0.9	$eGRF = 141 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$

White or other	> 0.9	$eGRF = 141 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$

Baseline eGFR will be obtained for all subjects (ie, subjects with renal impairment and matched-control healthy subjects) by taking the mean of the eGFR obtained from Screening and from historical values obtained within a 3-month period from Screening. If no historical eGFR value is available, a second Screening eGFR sample will be taken during the Screening period (≥ 14 days apart) and the mean of the 2 values will be used as the baseline eGFR for group assignment. Individual eGFR values recorded for each measurement contributing to the subject mean baseline value must fall within the specified eGFR ranges for each group (ie, matched-control healthy subjects and subjects with severe renal impairment [and subjects with mild and/or moderate renal impairment, if they are enrolled]) to categorize subjects' renal impairment status. The eGFR based on CKD-EPI equation will be repeated at Check-in (Day -1) to confirm renal impairment status. For matched-control healthy subjects, a single assessment of actual creatinine clearance computed over a 24-hour urine collection may be used in place of the eGFR (based on the CKD-EPI equation), at the Investigator's (or designee's) discretion.

Subjects with severe renal impairment (Group 4), and matched-control healthy subjects with normal renal function (Group 1) will begin enrolling in the study first. Subjects will be recruited so that up to 8 subjects with severe renal impairment and up to 8 subjects with normal renal function are enrolled, with the goal of having at least 6 subjects with severe renal impairment and at least 6 matched-control healthy subjects complete the study.

Subjects will be enrolled within the following groups based on their eGFR values calculated using the CKD-EPI equation at Screening and repeated at Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 1: Matched-control healthy subjects with normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2)
- Group 4: Subjects with severe renal impairment (eGFR: < 30 mL/min/1.73 m^2)

Continuous review of the safety data and PK data (if available) from up to 8 subjects with severe renal impairment and up to 8 matched-control healthy subjects with normal renal function will be conducted after these subjects have completed all study-related assessments through 72 hours (approximately 3 half-lives) postdose, at a minimum. The safety data will include AEs and serious AEs (SAEs), vital signs, physical examinations, ECGs, and clinical laboratory evaluations.

Following continuous review of the safety data and PK data from up to 8 subjects with severe renal impairment (Group 4) and up to 8 matched-control healthy subjects with normal renal function (Group 1), subjects with mild renal impairment (Group 2) and/or moderate renal impairment in (Group 3) may be enrolled if deemed necessary by the Sponsor. If no clinically relevant effect on PK is observed in subjects in Group 1 and Group 4, enrollment of subjects in Group 2 and/or Group 3 will not occur.

If the Sponsor deems it necessary to enroll subjects with mild and/or moderate renal impairment, subjects will be recruited so that up to 8 subjects with mild renal impairment, up

to 8 subjects with moderate renal impairment, and up to an additional 16 matched-control healthy subjects with normal renal function may be enrolled, with the goal of having at least 6 subjects with mild renal impairment and at least 6 subjects with moderate renal impairment and their matched-control healthy subjects complete the study. Enrollment and dosing for subjects in Group 2 and/or Group 3 may only occur after the safety and PK data for subject(s) in Group 1 and Group 4 through a minimum of 72 hours postdose are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Subjects will be enrolled within the following groups based on their eGFR values calculated using the CKD-EPI equation at Screening and repeated at Check-in (Day -1) as judged by the Investigator (or designee), Covance Medical Monitor, and Sponsor:

- Group 2: Subjects with mild renal impairment ($60 \leq$ eGFR < 90 mL/min/1.73 m^2)
- Group 3: Subjects with moderate renal impairment ($30 \leq$ eGFR < 60 mL/min/1.73 m^2)

Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the completed renal impairment subject(s). Should another renal impairment subject be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different renal impairment group. Each subject with normal renal function may be matched with up to 1 subject within each renal impairment group.

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

To assess their eligibility to enter the study, potential subjects will be screened within 28 days (Days -29 to -2) and will be admitted to the Clinical Research Unit (CRU) on Day -1 (Check-in). Subjects who are determined to be screen failures are permitted to be re-screened if the Investigator (or designee), with agreement from the Covance Medical Monitor and the Sponsor, feels that the subject may meet eligibility criteria upon re-screen. Re-screened subjects will be provided a new subject number.

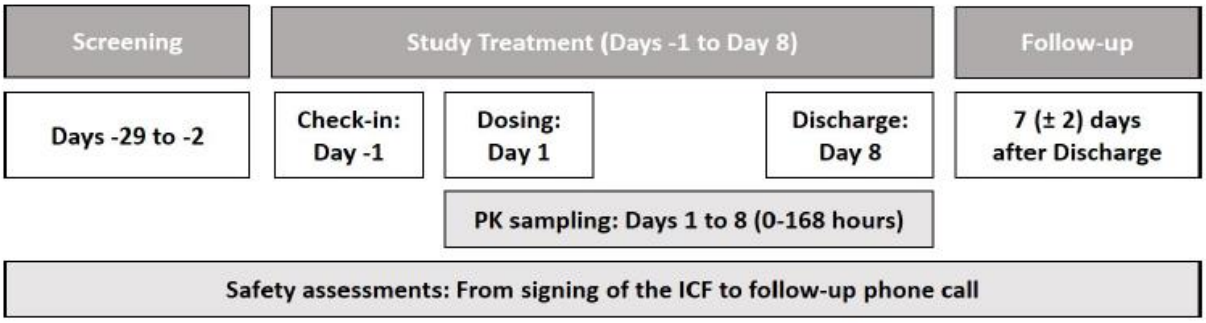
Subjects will be confined at the CRU from the time of Check-in (Day -1) until End of Treatment (EOT) on Day 8 upon completion of all PK and safety assessments or Early Termination (ET) if the subject discontinues. Subjects will be dosed on Day 1. A follow-up phone call will occur for all subjects who received a 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 up to 46 days (Screening through follow-up phone call).

On the morning of Day 1, after at least an 8-hour fast, a single oral dose of 200 mg LOXO-305 will be administered with approximately 240 mL of water. No food will be allowed for up to 2 hours postdose. Glucose tablets may be administered as needed for

treatment of hypoglycemia in renally impaired subjects with diabetes. PK samples will be obtained through 168 hours postdose.

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

Figure 1: Study Design



ICF = informed consent form; PK = Pharmacokinetics
Note: Single oral dose of LOXO-305 at 200 mg administered orally after at least an 8-hour fast.

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 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

A total of up to 24 subjects with renal impairment (up to 8 subjects with severe impairment, and, if necessary, up to 8 subjects with moderate impairment, and/or up to 8 subjects with mild impairment, per eGFR using the CKD-EPI equation) and approximately 8 to 24 matched-control healthy subjects with normal renal function will be enrolled in the study with the goal of having at least 6 subjects from each renal impairment group enrolled in the study and at least 6 subjects with normal renal function complete the study. The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and

was not based on power calculations to detect statistically significant differences among groups. This number is considered a sufficient sample size to evaluate the PK of LOXO-305 under various degrees of renal function.

6. STUDY TREATMENT AND RENAL FUNCTION GROUPS

The planned treatment administered for all subjects will be 200 mg LOXO-305.

The renal function group names and ordering to be used in the TFLs are presented in Table 2.

Table 2: Presentation of Renal Function Groups in TFLs

Renal Function Group	Abbreviation	Order in TFLs
Normal Renal Function	Normal	1
Mild Renal Impairment	Mild	2
Moderate Renal Impairment	Moderate	3
Severe Renal Impairment	Severe	4

All renal function groups described above are the planned groups. If the mild and moderate renal impairment groups are not enrolled, the subsequent order of the severe group will be amended. The TFLs will reflect the actual renal function groups dosed based upon their eGFR using the CKD-EPI equation.

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 1 dose of study drug. Subjects will be classified into renal function groups based off of their baseline eGFR value using the CKD-EPI equation.

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}. 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 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 3.1.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, and any parameter derivations.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

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

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a

given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.

- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 8.6.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

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

8.1.2. Repeat and Unscheduled 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 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.

Post dose repeats, unscheduled assessments, and ET measurements will be excluded from all calculations, with the exception of the baseline derivation (see Section 0).

8.1.3. Definitions of Baseline and Change from Baseline

Baseline value is defined as the last non-missing measurement before administration of LOXO-305.

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

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

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

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by renal function group will be provided, based on the all subjects population.

8.3. Demographics and Baseline Characteristics

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

A summary table by renal function group will be provided, based on the safety population.

The eGFR data will be listed and summarized.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to the dose of LOXO-305. Concomitant medication will be defined as medication that starts during or after the dose of LOXO-305 or starts but does not end prior to the dose of LOXO-305.

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

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

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

Parameter	Units[a]	Definition
AUC_{0-t}	h*ng/mL	area under the concentration-time curve from hour 0 to the last measurable concentration (t_{last})[b]
AUC_{0-inf}	h*ng/mL	area under the concentration-time curve from time 0 extrapolated to infinity[c]
$\%AUC_{extrap}$	%	percentage extrapolation for AUC_{0-inf}
C_{max}	ng/mL	maximum observed plasma concentration
t_{max}	h	time to maximum observed plasma concentration
λ_z	1/h	apparent terminal elimination rate constant
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent systemic clearance
V_z/F	L	apparent volume of distribution at the terminal phase
MRT_{inf}	h	mean residence time (based on AUC_{0-inf})
f_u	--	unbound fraction

[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

The unbound fraction (f_u) in plasma, expressed as a decimal, will be calculated from protein binding concentration data as the unbound drug concentration divided by the total drug concentration in plasma. The f_u value determined for each subject will be used to calculate the following unbound LOXO-305 PK parameters for each individual subject:

$C_{max,u}$	Unbound C_{max}, calculated as $C_{max}*f_u$
$AUC_{0-t,u}$	Unbound AUC_{0-t}, calculated as $AUC_{0-t}*f_u$
$AUC_{0-inf,u}$	Unbound AUC_{0-inf}, calculated as $AUC_{0-inf}*f_u$
$CL/F_{,u}$	Unbound CL/F, calculated as $Dose/AUC_{0-inf,u}$
$V_z/F_{,u}$	Unbound V_z/F, calculated as $CL/F_{,u}/\lambda_Z$

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-inf}, $t_{1/2}$, CL/F, V_z/F, and MRT_{inf}) 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 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}.

$AUC_{0\text{-}inf}$ values where the percentage extrapolation is less than 30% will be reported. $AUC_{0\text{-}inf}$ values where the percentage extrapolation is greater than 30% will be listed but excluded from descriptive statistics and 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 predose plasma concentration is missing, it may 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 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 and CV of geometric mean will be reported as not calculated (NC).

For PK parameters the following rule will apply:

- For the calculation of summary statistics of PK parameters, all not reported (NR) and not calculated (NC) values in a data series will be set to missing.
- The AUC values will be set to NC if they have been calculated using fewer than 3 concentrations, and/or 3 concentrations if the last is C_{max}.
- Geometric 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 renal function and time postdose will be provided for plasma PK concentrations. All PK concentration figures will be produced on both linear and semi-logarithmic scales. The +SD bars will only be displayed on the linear scale.

Summary tables by renal function will be provided for all PK parameters, with the exception of diagnostic regression-related PK parameters. Summary statistics (n, Mean, SD, CV, minimum, median, maximum, geometric mean [Geom Mean] and geometric CV [Geom CV]) will be calculated for plasma LOXO-305 PK parameters. A Figure of individual PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) and corresponding unbound PK paramaters and corresponding geometric mean of PK parameters figures by renal function will be provided. 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.

The primary analysis planned for this study is to evaluate the PK of LOXO-305 after a single dose in subjects with renal impairment compared to subjects with normal renal function.

Paired t-tests will be performed to assess the differences in PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) and corresponding unbound PK parameters between each renal impairment group versus the corresponding matched-control healthy group with respect to 1 to 1 matching. The analysis will be based on the natural log (ln)-transformed PK parameters. Geometric mean ratios and their corresponding 90% confidence intervals (CIs) will be calculated using the exponentiation of the mean difference and the CIs obtained for the difference in mean between each renal impairment group and the matching healthy control group.

Paired t-test Analysis:

```
proc ttest data = <data in> alpha=0.1;
  by parcat1 paramn paramcd;
  paired logaval&test.*logaval&ref.;
  ods output statistics = <data out>;
  ods output ttests = <data out>;
```

```
run;
```

In addition, an analysis of covariance (ANCOVA) will be performed on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. The ANCOVA model will contain a categorical factor of population for subjects with varied-degree renal impairment (severe, moderate, and mild) and matched-control healthy subjects, a categorical covariate (sex), and continuous covariates (age and BMI). Ratios of least squares means (LSM) and 90% CIs will be calculated using the exponentiation of the difference between renal function cohort LSM from the ANCOVA analyses on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. In addition, an ANCOVA will be performed on the ln-transformed $AUC_{0-t,u}$, $AUC_{0-inf,u}$, and $C_{max,u}$.

ANCOVA Analysis:

```
proc mixed data = <data in>;
  by parcat1 paramn paramcd;
  class &renimp sex;
  model laval = &renimp sex age bmi / alpha=0.1 cl outp=pred residual
  ddfm=kr;
  lsmeans &renimp / cl pdiff=control('1') alpha=0.1;
  ods output lsmeans = <data out>;
  ods output diffs = <data out>;
  ods output covparms = <data out>;
run;
```

The relationship between LOXO-305 PK parameters (ie, C_{max} and AUC) and measures of renal function (such as eGFR and creatinine clearance) may be explored using a linear regression approach or other methods. The effect of covariates such as age, BMI, and sex may be investigated.

Additionally, a scatterplot of the ln-transformed PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) and corresponding unbound PK paramaters versus eGFR be produced. The linear regression will be included on the plot, along with two-sided 90% confidence bands for the linear regression line. The Spearman rank correlation coefficient will also be calculated..

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. All AEs will be assigned severity grade using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after LOXO-305 dosing, or starts prior to LOXO-305 dosing and increases in severity after LOXO-305 dosing.

A treatment-related TEAE will be defined as a TEAE with a relationship of related to the study treatment (LOXO-305), as determined by the investigator.

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

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

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

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

- System organ class, preferred term, and renal function group
- Preferred term and renal function group

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to dosing.
- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).
- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

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

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, with 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, with changes from baseline will be summarized descriptively by renal function group and timepoint.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, and calculation of summary statistics, <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 results will be summarized descriptively by renal function group 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 renal function group and timepoint. For the mild renal impairment, moderate renal impairment and Healthy subjects QTcF values that are > 450 msec and increase from baseline > 30 msec will be flagged in the data listing. For severe renal impairment subjects 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

Subjects with renal impairment assessed as severe, along with matched-control healthy subjects, will begin enrolling in the study first. Continuous review of the safety data and PK data (if available) from up to 8 subjects with severe renal impairment and up to 8 matched-control healthy subjects with normal renal function will be conducted after these subjects have completed all study-related assessments through 72 hours (approximately 3 half-lives) postdose, at a minimum. The safety data will include AEs and SAEs, vital signs, physical examinations, ECGs, and clinical laboratory evaluations.

If a clinically relevant difference is observed in the PK of subject(s) with severe renal impairment compared to matched-control healthy subjects during continuous review of the safety and PK data, then subjects with renal impairment assessed as mild ($60 \leq$ eGFR < 90 mL/min/1.73 m^2) and/or moderate ($30 \leq$ eGFR < 60 mL/min/1.73 m^2), along with additional matched-control healthy subjects (if needed) will be enrolled, to determine the extent of the effect of varying severities of renal impairment on the PK of LOXO-305. Enrollment of subjects with mild and/or moderate renal impairment will only be initiated if deemed necessary by the Sponsor following the continuous review of safety and PK data from severe renal impairment subjects and their matched-control healthy subjects. If no clinically relevant effect on PK is observed, enrollment of mild and/or moderate subjects will not occur.

Enrollment and dosing for remaining subjects in Group 2 and/or Group 3 may only occur after the data for Group 1 and Group 4 are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Subjects will be recruited for Group 2 and/or Group 3 so that up to 8 subjects with mild renal impairment, up to 8 subjects with moderate renal impairment, and up to an additional 16 matched-control healthy subjects with normal renal function may be enrolled, with the goal of having at least 6 subjects with mild renal impairment and at least 6 subjects with moderate renal impairment and their matched-control healthy subjects complete the study.

Teleconferences will occur as needed between the Covance Medical Monitor, Investigator (or designee), and Sponsor to discuss PK, safety, and tolerability data.

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. Levey A, Stevens L, Schmid C, Zhang Y, Castro A, Feldman H, et al. A new equation to estimate glomerular filtration rate. Ann intern med. 2009;150(9): 604-12.

12. APPENDICES

Appendix 1: Document History

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

NA = not applicable

Statistical Analysis Plan (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-20013	**Covance Study ID:**	8419692
SAP text filename:	LOXO-BTK-20013_SAP_Sponsor_Final_V1.0.docx		
TFL shells filename:	LOXO-BTK-20013_TFL_Shells_Sponsor_Final_V1.0.docx		
Version:	Final Version 1.0	**Date:**	08 March 2021

Covance Approval(s):

Lead Statistician

Approval Signature	PPD
Print Name	
Job Title	
Date	

Lead Pharmacokineticist

Approval Signature	PPD
Print Name	
Job Title	
Date	

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the 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	PPD
Print Name	
Job Title	
Date	08-Mar-21 | 14:05:00 PST

Please scan/email compl listed below:

Printed Name/Title:	
Email:	