Statistical Analysis Plan J2G-OX-JZJD

Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

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16.1.9. Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

Open-label, Nonrandomized, Single-dose, Parallel-group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-292 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-control Healthy Subjects

Statistical Analysis Plan Status: Final 1
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Study Drug: LOXO-292

Sponsor Reference Number: LOXO-RET-18022
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Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

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Date

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Pharmacokineticist

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2 TABLE OF CONTENTS

1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES 2
2 TABLE OF CONTENTS 3
3 ABBREVIATIONS 5
4 INTRODUCTION 8
5 STUDY OBJECTIVE 8
6 STUDY DESIGN 8
7 TREATMENTS 10
8 SAMPLE SIZE JUSTIFICATION 11
9 DEFINITION OF ANALYSIS POPULATIONS 11
10 STATISTICAL METHODOLOGY 11
10.1 General 11
10.1.1 Definition of Baseline and change from baseline 12
10.1.2 Repeat and Unscheduled Readings 12
10.2 Demographics and Subject Disposition 12
10.3 Pharmacokinetic Assessment 13
10.3.1 Pharmacokinetic Parameters 13
10.3.2 Criteria for Handling Plasma Concentrations Below the Limit (CBLL) of Quantification 14
10.3.3 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life 14
10.3.4 Calculation of AUC 15
10.3.5 Anomalous Values 15
10.3.6 Handling Rules for Missing or BLQ Values 15
10.4 Statistical Methods for Pharmacokinetic Data 16
10.4.1 Descriptive Statistics 16
10.4.2 Primary Analysis 16
10.4.3 Analysis of Covariance 17
10.5 Safety and Tolerability Assessments 18
10.5.1 Adverse Events 18
10.5.2 Clinical Laboratory Parameters 18
10.5.3 Vital Signs 19
10.5.4 Electrocardiogram 19
10.5.5 Other Assessments 20
10.5.6 Safety and Tolerability Statistical Methodology 20

11 INTERIM ANALYSES 20
12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES 20
13 DATA PRESENTATION 21
13.1 Insufficient Data for Presentation 21
14 REFERENCES 21

3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	analysis data model
AE	adverse event
ANCOVA	analysis of covariance
$\%AUC_{extrap}$	percentage extrapolation for area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
$AUC_{0-\infty,u}$	unbound area under the concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{0-t,u}$	unbound area under the concentration-time curve from time 0 to the last measurable concentration
BLQ	below the limit of quantification
BMI	body mass index
CBC	Complete Blood Count
CDISC	Clinical Data Interchange Standards Consortium
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 concentration
CP	Child-Pugh
CSR	Clinical Study Report
CV%	coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
f_u	fraction unbound in plasma
ICF	Informed consent
ICH	International Conference on Harmonisation
LLOQ	lower limit of quantification
λ_Z	apparent terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{last}	Mean residence time
NC	Not calculated
NR	No result
PE	Physical examination
PK	Pharmacokinetic
PT	preferred term

QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time to maximum observed concentration
V_d/F	apparent volume of distribution during the terminal phase
$V_d/F_{,u}$	unbound apparent volume of distribution during the terminal phase

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 15 October 2018).

This SAP describes the planned analysis of the safety, tolerability and PK 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 shell document.

The intent of this document is to provide guidance for the statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Loxo Oncology, Inc. and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning 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 agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the 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 in the CSR. Any substantial deviations from this SAP will be agreed upon between Loxo Oncology, Inc. and Covance EC Biometrics and identified in the CSR.

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

5 STUDY OBJECTIVE

The objectives of this study are:

- To evaluate the PK profile of LOXO-292 in subjects with impaired hepatic function compared to matched-control healthy subjects;

- To evaluate safety and tolerability of LOXO-292 in subjects with impaired hepatic function and matched-control healthy subjects.

6 STUDY DESIGN

This study will be an open-label, nonrandomized, multi-center, single-dose, parallel-group, safety, tolerability, and PK study of LOXO-292 administered orally at a dose of 160 mg in fasted matched control healthy males and females with normal hepatic function compared to fasted, hepatically impaired subjects.

Subjects will be recruited in this study so that up to 24 subjects with hepatic impairment (up to 8 subjects within each of the mild, moderate, and severe impairment groups, per Child-Pugh [CP] classification – assessed at Screening and Check-in [Day -1]), and approximately 8 to 16 subjects with normal hepatic function are enrolled. Subjects will be enrolled within the following groups based on their CP score at Screening and assuming no change in underlying hepatic status at Check-in (Day -1) as judged by the Investigator (or designee), the Covance Medical Monitor, and the Sponsor:

- Group 1: Matched-control healthy subjects with normal hepatic function;
- Group 2: Subjects with mild hepatic impairment (CP Class A, score of 5 or 6);
- Group 3: Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9);
- Group 4: Subjects with severe hepatic impairment (CP Class C, score of 10 to 15).

A parallel design strategy will be adopted for the hepatic impairment groups, with interim reviews of safety data after the first 4 subjects from Group 2 (mild hepatic impairment subjects), the first 4 subjects from Group 3 (moderate hepatic impairment subjects), and the first 2 subjects from Group 4 (severe hepatic impairment subjects) are enrolled and have completed all study-related assessments including the Follow-up phone call. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing. If available, PK data and matched-control healthy subject data may also be used during the interim review.

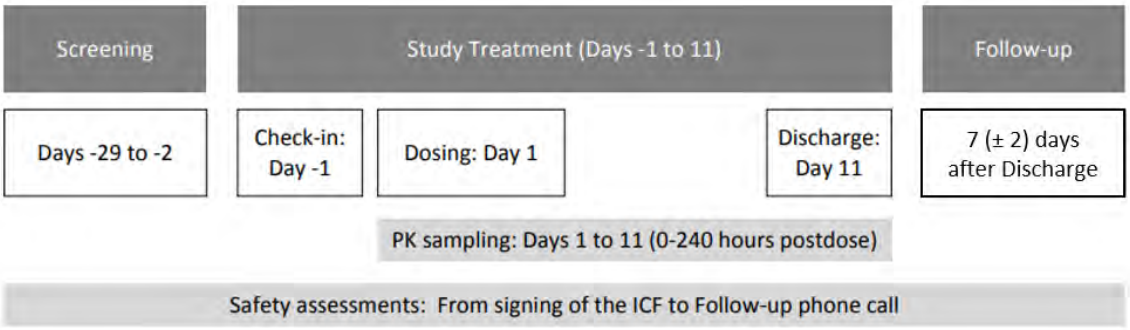
Each matched-control healthy subject (Group 1) will be demographically matched (1:1) by age (± 10 years), body mass index (BMI; ± 20%), and sex to the enrolled hepatic impairment subject(s). Should another hepatic impairment subject be identified with whom an already enrolled healthy subject is demographically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

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 site on Day -1 (Check-in). Replacement subjects may be enrolled only if deemed necessary by the Sponsor.

Subjects will be confined at the clinical site from the time of Check-in (Day 1) until Clinic Discharge on Day 11 upon completion of all PK and safety assessments. A Follow-up phone call will occur approximately 7 days after Clinic Discharge.

On the morning of Day 1, after at least a 2-hour fast, an oral dose of 160 mg LOXO 292 administered as two 80-mg capsules will be given with 240 mL water. No food will be allowed for up to 1 hour postdose. Glucose tablets may be administered as needed for treatment of hypoglycemia.

Figure 1 Study design schematic



ICF = Informed Consent Form; PK = pharmacokinetic.
Note: Single oral dose of LOXO-292 at 160 mg administered orally after at least a 2-hour fast.

In this study design, physical examinations (PEs), 12-lead electrocardiograms (ECGs), vital signs, How Do You Feel? inquiries, clinical chemistry panel, coagulation parameters, complete blood count, and urinalysis will be performed at Screening and at specified times during the study. All adverse events (AEs) will be recorded throughout the study (ie, from signing of the ICF until Study Completion), either as subject medical history (if the event is reported as occurring prior to signing of the ICF) or as AEs (if the event occurs after administration of LOXO-292). Between the time of ICF signing to administration of LOXO-292 only AEs assessed as related to study procedures should be reported. All serious AEs (SAEs) that develop from the time of ICF signing until Study Completion are to be reported.

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

7 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs

Hepatic Function Designation	Child-Pugh Classification	Study Treatment Name	Abbreviation	Order on TFLs
Normal Hepatic Function	< 5 points	Single dose of 160 mg LOXO-292	160 mg LOXO-292	1
Mild Hepatic Impairment	5 or 6 points (Class A)	Single dose of 160 mg LOXO-292	160 mg LOXO-292	2
Moderate Hepatic Impairment	7 to 9 points (Class B)	Single dose of 160 mg LOXO-292	160 mg LOXO-292	3
Severe Hepatic Impairment	10 to 15 points (Class C)	Single dose of 160 mg LOXO-292	160 mg LOXO-292	4

8 SAMPLE SIZE JUSTIFICATION

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. Six subjects each per hepatic function group are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of LOXO-292 under various degrees of hepatic function.

9 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug (LOXO-292) and have at least 1 post dose safety assessment.

The PK population will comprise all subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations). Samples from all subjects will be assayed even if the subjects do not complete the study. PK population will comprise all subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations). A subject who experiences emesis at or before 2 times median Tmax for the given treatment during the PK sampling period time course may be excluded from the PK summary statistics and statistical analysis

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

The **All Subjects Populations** will consist of any subjects who enrolled on to the study (signed informed consent, met all inclusion and exclusion criteria, and had study assessments recorded on the database as per the protocol).

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum, and number. For log-normal data (eg, the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [Cmax]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects

excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

10.1.1 Definition of Baseline and change from baseline

Baseline for each parameter is defined as the last non-missing value measured prior to dosing, including repeat (vital signs andECGs and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings).

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires a recheck. Repeat readings are labelled as 'Repeat' in the listings. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Unscheduled post-dose repeat readings will not be used in the summarization and calculations."

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and BMI will be summarized and listed by hepatic function group. The CP score will be listed. Subject disposition will be summarized and listed by hepatic function group.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Parameters

The following PK parameters will be determined where possible from the plasma concentrations of LOXO-292 using non-compartmental methods performed using Phoenix WinNonlin (Certara USA, Inc.) version 6.4 or higher:)

Parameter	Definition
C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
AUC_{0-t}	area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing and decreasing concentrations
$AUC_{0-\infty}$	AUC extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage extrapolation for AUC
λ_Z	apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus-time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (ln)(2)/λ_Z
CL/F	apparent systemic clearance
V_d/F	apparent volume of distribution during the terminal phase
MRT_{last}	mean residence time

Based on data from in vitro equilibrium dialysis study of a sample of pre-dose plasma from each subject, spiked with LOXO-292, the unbound fraction (fu) in plasma, expressed as a decimal, will be calculated from protein binding concentration data as the unbound drug concentration (concentration in buffer chamber) divided by the total drug concentration in plasma (concentration in the plasma chamber). The fu value determined for each subject will be used to calculate the following unbound LOXO 292 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 $AUC_{0-t}*f_u$

$AUC_{0-\infty,u}$ Unbound $AUC_{0-\infty}$, calculated as $AUC_{0-\infty}*f_u$

$CL/F,_u$ Unbound CL/F, calculated as $Dose/AUC_{0-\infty,u}$

$V_d/F,_u$ Unbound V_d/F, calculated as $CL/F,_u/\lambda_Z$

Additional PK parameters may be determined where appropriate. The number of points used to estimate λ_Z, the lower and upper limits of the points used in estimation, and the adjusted coefficient for determination of exponential fit (R^2 adjusted) will be presented in a listing.

PK analysis will, where possible, be carried out using actual times recorded in the raw data . If actual times are missing, nominal times may be used with sponsor approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles. For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

10.3.2 Criteria for Handling Plasma Concentrations Below the Limit (CBLL) of Quantification

Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows:

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

If a predose concentration is missing, these values are set to zero in PK analysis by default within Phoenix WinNonlin.

10.3.3 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

Number of Data points

At least three data points will be included in the regression analysis and preferably should not include C_{max}.

Goodness of fit

When assessing terminal elimination phases, the R^2 adjusted value will be used as a measure of the goodness of fit of the data points to the determined line.

Regression-based parameters ($AUC_{0-\infty}$, λ_Z, $t_{1/2}$, CL/F, and $V_{d/F}$) will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7

Period of Estimation

Time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives.

Where an elimination half-life is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the study report.

10.3.4 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following Cmax.
- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is between 20 to 30% will be flagged and included in the descriptive statistics, whilst $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be reported but excluded from descriptive statistics.

10.3.5 Anomalous Values

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

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

- Positive predose value(s) greater than 5% of Cmax may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

10.3.6 Handling Rules for Missing or BLQ Values

For Pharmacokinetic Plasma Drug Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (eg, no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are fewer than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

For Pharmacokinetic Parameters:

For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

10.4 Statistical Methods for Pharmacokinetic Data

10.4.1 Descriptive Statistics

Arithmetic means, %CV, SD, median, Min, Max, and n will be calculated for PK parameters separately in healthy subjects and subjects with hepatic impairment. Geometric mean and geometric %CV will be provided for all PK parameters except t_{max}. Median, min, max, and n will be calculated for t_{max}. In addition, summary statistics for protein binding will be tabulated by hepatic function group.

10.4.2 Primary Analysis

To evaluate the effect of hepatic function group on the PK of a single dose of LOXO-292, paired t-test will be performed for each hepatic impairment group versus the normal group with respect to 1 to 1 matching. The 1 to 1 matching comparisons of interests include:

- Subjects with severe hepatic impairment versus healthy matched control subjects.

- Subjects with moderate hepatic impairment versus healthy matched control subjects.
- Subjects with mild hepatic impairment versus healthy matched control subjects.

Since the comparison groups of subjects are independent in terms of degrees of hepatic impairment and dependent based on the matching criteria, paired Proc ttest in SAS will be used for this comparison on the natural log transformed PK parameters (AUC0-t, AUC0-∞, and Cmax). The 90% confidence interval for the ratio between each level of impaired hepatic function versus the matched-control healthy subject group will be presented. The normality assumption will be explored to ensure no major deviation to the assumption exists. The corresponding results along with any outliers will be evaluated and can be included in the CSR appendix as needed. Any major outliers will be investigated case by case and determine the appropriate action on how to handle them.

Example SAS code:

```
proc ttest data= logpk alpha=0.1;
by paramcd;
paired normal*impairment;
run;
```

where;
paramcd = categorical variable to indicate different PK parameters
impairment= natural log-transformed PK parameters for the subjects with hepatic impairment
normal= natural log-transformed PK parameters for the healthy matched controlled subjects

10.4.3 Analysis of Covariance

To evaluate the effect of hepatic function group on the PK of a single dose of LOXO-292In addition, an analysis of covariance (ANCOVA) will be performed on the natural log transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The ANCOVA model will contain a categorical factor of population for subjects with various degrees of hepatic impairment (mild, moderate, and severe) and healthy matched control subjects, a categorical covariate (sex), and continuous covariates (age and BMI). The ratios of least square means (LSM) and 90% CI for the ratio of the PK parameter for each hepatic function group versus the matched normal group will be constructed using the exponentiation of the difference and the CIs from the ANCOVA analyses. These ratios will be expressed as a percentage relative to the healthy matched control cohort.

The 1 to 1 matching comparisons of interests include:

- Subjects with severe hepatic impairment versus healthy matched control subjects.
- Subjects with moderate hepatic impairment versus healthy matched control subjects.
- Subjects with mild hepatic impairment versus healthy matched control subjects.

Example SAS code:
proc mixed data = dataset;
class group sex;
model lPK = group sex age BMI / alpha=0.1 cl solution outpred=resids;
lsmeans group / pdiff alpha=0.1;
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;
quit;

Residual plots will be produced to assess the adequacy of the model.

10.5 Safety and Tolerability Assessments

10.5.1 Adverse Events

All safety data will be listed by subject. All AEs occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 21.0. A baseline sign and symptom is defined as an AE that starts after the subject has provided written informed consent and that resolves prior to the receipt of first dose of study drug, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose. The severity of AEs will be categorized based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 2-category system (i.e. Not Related or Related). Onset times postdose are calculated from the last dose administered. The AE severity and relationship are determined by the investigator at the site.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, part, severity grade, relationship to study treatment, outcome, and action. TEAEs, drug-related TEAEs, and TEAEs by severity will be summarized by each hepatic function group. The frequency of TEAEs (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) will be summarized by each hepatic function group, and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of 'RELATED'). Any severe TEAEs, serious TEAEs (SAEs), or TEAEs leading to discontinuations will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

10.5.2 Clinical Laboratory Parameters

Clinical chemistry, hematology and coagulation data will be summarized by hepatic function group and timepoint. Changes from baseline will be calculated. In addition, all Clinical

Chemistry, CBC, hematology, coagulation and urinalysis data outside the clinical reference ranges will be listed by parameter and hepatic function group.

Values for any clinical chemistry, hematology, coagulation and urinalysis values outside the clinical reference ranges will be flagged on the individual subject data listings. Reference ranges will be presented in the listing and used to determine either the low or high values in comparison to the reference ranges. Hemoglobin A1c Test Data will be listed by Subject.

All out of range laboratory evaluation data (including clinical chemistry, hematology, and urinalysis) deemed clinically relevant by the PI (or designee) will be listed by parameter.

10.5.3 Vital Signs

The vital signs data (including oral temperature, supine blood pressure, heart rate, and respiratory rate) will be summarized by hepatic function group and time point, together with changes from baseline. Figures of mean vital signs and mean change from baseline profiles will be presented by hepatic function group.

Vital signs values outside the clinical reference ranges will be flagged in the individual subject data listings.

Repeat and unscheduled readings will be handled as defined in Section 10.1.2

10.5.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, and heart rate.

The ECG data along with change from baseline will be listed and summarized by timepoint.

Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listings.

An outlier analysis will be performed including all maximum individual postdose measurements (not the mean data), including all repeat and unscheduled readings. All incidences of QTc and QTcF (>450 and ≤ 480, >480 and ≤ 500, and >500 ms) will be flagged in the listings. Change of > 30msec in QTcF will be flagged.

10.5.5 Other Assessments

PE and concomitant medications(coded using WHODrug Version 01 September 2018 Global Dictionary DDE+HD Version B3 format) will be listed by hepatic function group and time point using descriptive statistics.

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

Medical history data will be presented.

10.5.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

Interim reviews of safety data will be conducted for each group when the first 4 subjects from Group 2 (mild hepatic impairment subjects) are enrolled and have completed the study, when the first 4 subjects from Group 3 (moderate hepatic impairment subjects) are enrolled and have completed the study, and when the first 2 subjects from Group 4 (severe hepatic impairment subjects), are enrolled and have completed the study. Subjects will be considered to have completed the study if they have undergone all study-related assessments as described in the Schedule of Assessments, including the Follow-up phone call. These safety data will include AEs and serious AEs, vital signs, PEs, ECGs, and clinical laboratory tests. If available, PK data and matched-control healthy subject data may also be used during the review. Enrollment and dosing for remaining subjects in any group may occur after the interim data for that group are reviewed and the Covance Medical Monitor, Investigator (or designee), and Sponsor agree it is safe to proceed with dosing.

Each interim review will be a teleconference between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor to discuss safety data.

Following the interim review of safety data for a group, the dose level may be decreased for the remaining subjects in any group pending discussion and agreement between the Covance Medical Monitor, Investigator (or designee), and/or Sponsor. If dosing is decreased, it will also be decreased for the impaired subjects' respective matched-control healthy subjects.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

The statistical methods for analysing the PK data outlined in the synopsis and main body of the protocol (version 1.0) and have been clarified in further detail in Sections 10.4.2 and 10.4.3, including an additional analysis suitable for the hepatic design of the trial.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.