Statistical Analysis Plan: J2G-OX-JZJG

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

NCT05630274

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16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

Statistical Analysis Plan

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

Protocol No: LOXO-RET-18032
Final Protocol Date: 03 April 2019
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Compound Name: LOXO-292

Celerion Project CA25494
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Loxo Oncology, Inc.
701 Gateway Boulevard, Suite 420
South San Francisco, California 94080, USA

Celerion
621 Rose Street
Lincoln, Nebraska 68502, USA
And
100 Alexis-Nihon Boulevard, Suite 360,
Montreal, QC H4M 2N8, Canada

Statistical Analysis Plan Signature Page

Compound Name: LOXO-292

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Study Title: A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

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Director, Biostatistics, Data Management and Biometrics
Celerion, PPD USA

Signature: PPD Date: 04-JUL-2019

PPD Clinical Pharmacology and Pharmacometrics, Data Management and Biometrics
Celerion, PPD Canada

Signatur PPD Date: 11-Jul-19 | 17:41:16 PDT

California, USA

Table of Contents

1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from study LOXO-RET-18032 which will be analyzed by Celerion. The SAP may change due to unforeseen circumstances. Any changes made from the planned analysis within the protocol or after the locking of the database will be documented in the clinical study report (CSR). The section referred to as Table Shells within this SAP describes the traceability of the tables, figures, and listings (TFLs) back to the data. Note that the header for this page will be the one used for the main body of the CSR.

Any additional analyses not addressed within this SAP and/or driven by the data, or requested by Loxo Oncology, Inc., will be considered out of scope and will be described in the CSR as needed.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Celerion will only assess the 3rd and 4th secondary objectives which are bolded below. All other objectives will be assessed by ERT (eResearchTechnology, Inc.) in a separate SAP and study report.

Primary:

To evaluate the effects of therapeutic and supratherapeutic exposure of LOXO-292 on the heart rate-corrected (QTc) interval by assessing concentration-QT (C-QT) relationship using exposure-response modelling.

Secondary:

To assess the effect of therapeutic and supratherapeutic exposure of LOXO-292 on other electrocardiogram (ECG) parameters.

To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control in healthy adult subjects.

To evaluate the pharmacokinetics (PK) of therapeutic and supratherapeutic doses of LOXO-292 in healthy adult subjects.

To evaluate the safety and tolerability of therapeutic and supratherapeutic doses of LOXO-292 dose in healthy adult subjects.

2.2 Endpoints

The cardiodynamic endpoints will be addressed will be addressed by ERT.

Pharmacokinetics:

The following PK parameters will be calculated for LOXO-292 and moxifloxacin: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, and t½.

Safety:

Safety endpoints will include 12-lead ECGs, physical examinations, vital signs, clinical laboratory tests, and adverse events (AEs).

3. STUDY DESIGN

This is a single-dose, randomized, double-blind (except for the use of moxifloxacin), placebo- and positive-controlled, 4-way crossover study.

Thirty-two (32), healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled.

Screening of subjects will occur within 28 days prior to the first dosing.

On Day 1, subjects will be randomized to 1 of 4 treatment sequences.

On Day 1 of each period, subjects will receive one of two single oral dose levels of LOXO-292, a single oral dose of moxifloxacin, or a single oral dose of LOXO-292 matching placebo on one occasion, according to a randomization scheme. Cardiodynamic samples will be collected predose and for up to 24 hours postdose. PK samples will be collected predose and for up to 24 hours postdose for moxifloxacin and up to 240 hours postdose for LOXO-292, as per treatment received.

There will be a washout period of 10 days between dosing in each period.

Safety and tolerability will be assessed through End of Treatment (EOT) or Early Termination (ET) by monitoring AEs, performing physical examinations and clinical laboratory tests, measuring vital signs, and recording ECGs.

Subjects who do not complete the study treatments will not be replaced.

Subjects will be housed through EOT or ET beginning in Period 1, Day -1, at the time indicated by the clinical research unit (CRU), until after completion of study procedures in Period 4, Day 11 (EOT) or ET study procedures.

The CRU will contact all subjects who received at least one dose of study drug (including subjects who terminated the study early [ET]) at the End of Study (EOS) by a follow up (FU) phone call. The EOS/FU phone call will be performed 7 ± 2 days after the EOT visit or ET visit to determine if any SAE or study drug related AE has occurred since the EOT or ET visit.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Safety Population

All subjects who received at least one dose of either of the study drugs will be included in the safety evaluations.

Pharmacokinetic Population

Samples from all subjects will be assayed even if the subjects do not complete the study. 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) will be included in the statistical analyses.

Data for each subject will be included in the summary statistics and statistical comparisons of PK parameters with the exceptions described as follows:

- Data from subjects who experience emesis at or before 2 times median Tmax for the given treatment during the PK sampling period time course of the study for LOXO-292 or moxifloxacin may be excluded from the summary statistics for the given treatment and from the statistical comparison of PK parameters.
- Data from subjects who significantly violate a protocol inclusion or exclusion criterion, deviate significantly from the protocol, or have unavailable or incomplete data that may influence the PK analysis will be excluded from the PK Population.

Any subject or data excluded from the analysis will be identified, along with their reason for exclusion, in the CSR.

4.2 Preliminary Data and Interim Analysis

No interim analysis is planned for this study.

5. TREATMENT DESCRIPTIONS

LOXO-292 will be supplied as CCI mg CCI .

LOXO-292 matching placebo will be supplied as CCI .

Moxifloxacin will be supplied as CCI mg Avelox® (moxifloxacin hydrochloride) or generic equivalent CCI .

Treatments are described as follows:

Treatment A: CCI mg LOXO-292 (CCI CCI mg CCI) and LOXO-292 matching placebo (CCI cc mg matching placebo CCI) administered at Hour 0 on Day 1.

Treatment B: CCI mg LOXO-292 (CCI CCI mg CCI) administered at Hour 0 on Day 1.

Treatment C: CCI mg moxifloxacin (1 x CCI mg CCI) administered at Hour 0 on Day 1.

Treatment D: LOXO-292 matching placebo (CCI cc mg matching placebo CCI) administered at Hour 0 on Day 1.

Each treatment will be administered orally following a fast of at least 10 hours from food (not including water), with approximately 240 mL of water. Subjects will remain CCI (not including water) for at least 4 hours postdose.

Subjects will be instructed not to crush, split, or chew the CCI or the CCI .

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject and for each study period.

Table 5.1 Treatment Description

Treatment	Short Description (text, figure legends, SAS output)	Description (listings footnotes, in-text and post-text tables footnotes)
A	CCI mg LOXO-292	CCI mg LOXO-292 (CCI CCI mg CCI) and LOXO-292 matching placebo (CCI cc mg matching placebo CCI) administered at Hour 0 on Day 1

B	CCI mg LOXO-292	CCI mg LOXO-292 (CCI CCI mg CCI) administered at Hour 0 on Day 1
C	CCI mg moxifloxacin	CCI mg moxifloxacin (1 x CCI mg CCI) administered at Hour 0 on Day 1
D	LOXO-292 matching placebo	LOXO-292 matching placebo (CCI CC mg matching placebo CCI) administered at Hour 0 on Day 1

6. PHARMACOKINETIC ANALYSIS

6.1 Measurements and Collection Schedule

PK samples will be collected predose and for up to 24 hours postdose for moxifloxacin and up to 240 hours postdose for LOXO-292.

Blood samples for PK assessment of LOXO-292 will be taken at the following time points for Treatments A, B, and D: at predose and 0.25, 0.5, 0.75, 1.5, 2, 2.5, 3, 4, 7, 9, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose.

Blood samples for PK assessment of moxifloxacin will be taken at the following time points for Treatment C: at predose and 0.25, 0.5, 0.75, 1.5, 2, 2.5, 3, 4, 7, 9, 12, and 24 hours postdose.

All concentration data will be included in the calculation of the individual PK parameters, the individual concentration-time plots (based on actual sample times), and in the mean concentration-time plots (based on nominal sample times). However, if there are any significant deviations from nominal sample times, some concentration data may be excluded from mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be provided and discussed in the CSR.

6.2 Bioanalytical Method

6.2.1 LOXO-292

Plasma concentrations of LOXO-292 in Treatments A, B, and D will be determined using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method validated with respect to accuracy, precision, linearity, sensitivity, and specificity at

Alturas Analytics, Inc. (Moscow, Idaho, USA). The analytical range (lower limit of quantitation [LLOQ] – upper limit of quantitation [ULOQ]) for LOXO-292 in plasma is 1 – 1000 ng/mL. Samples that contain concentrations greater than 1000 ng/mL may be diluted up to 51-fold, if necessary, to be within the quantification range.

6.2.2 Moxifloxacin

Plasma concentrations of moxifloxacin in Treatment C will be determined using a LC-MS/MS method validated with respect to accuracy, precision, linearity, sensitivity, and specificity at Alturas Analytics, Inc. (Moscow, Idaho, USA). The analytical range (LLOQ – ULOQ) for moxifloxacin in plasma is 25 – 25000 ng/mL.

6.3 Investigational Product and PK Analyte Information

6.3.1 LOXO-292

LOXO-292 will be supplied as a simple blend with excipients containing CCI mg of drug substance (freebase) in a hard gelatin capsule.

6.3.2 Moxifloxacin

Moxifloxacin will be supplied as a CCI containing CCI mg drug substance.

6.4 Pharmacokinetic Concentrations

Plasma concentrations of LOXO-292 and moxifloxacin as determined at the collection times and per the bioanalytical methods described in Section 6.1 and Section 6.2, respectively, will be used for the calculation of the plasma LOXO-292 and moxifloxacin PK parameters.

6.5 Noncompartmental Pharmacokinetic Analysis and Parameter Calculation for LOXO-292 and Moxifloxacin

The appropriate noncompartmental PK parameters will be calculated from the plasma LOXO-292 and moxifloxacin concentration-time data using Phoenix® WinNonLin® Version 7.0 or higher. Actual sample collection times will be used in the calculations of the PK parameters. The calculation of the actual time for LOXO-292 and moxifloxacin will be in respect to the administration time of the LOXO-292 and moxifloxacin dose, respectively. All PK parameters included in the protocol are listed in Table 6.1 below, and are defined as appropriate for study design.

Table 6.1. Noncompartmental Pharmacokinetic Parameters to be Calculated for LOXO-292 and Moxifloxacin

Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
AUC0-t	Area under the concentration-time curve from time 0 to the time of the last observed non-zero concentration	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity	Calculated as AUC0-t + (Clast/Kel) where Clast is the last observed/measured concentration
AUC%extrap	Percent of AUC0-inf extrapolated	Calculated as 1-(AUC0-t/AUC0-inf)*100
Cmax	Maximum observed concentration	Taken directly from bioanalytical data
Tmax	The time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the Cmax.
Kel	Apparent terminal elimination rate constant; represents the fraction of drug eliminated per unit time	Calculated as the negative of the slope of a linear regression of the log(concentration)-time for all concentrations >LLOQ during the terminal elimination phase
t½	Apparent first-order terminal elimination half-life	Calculated as 0.693/Kel

PK parameters will not be calculated for subjects with fewer than 3 consecutive postdose time points with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only and excluded from all statistical analysis.

For the calculation of the PK parameters and PK concentrations summary statistics, plasma concentrations below the limit of quantitation (BLQ) prior to the first quantifiable concentration of a PK profile will be set to 0 and plasma concentrations BLQ after the first quantifiable concentration of a PK profile will be treated as missing.

The Kel will be determined using linear regressions composed of least 3 data points. The Kel will not be assigned if 1) the terminal elimination phase is not apparent, 2) if Tmax is one of the 3 last data points, or 3) if the R^2 value is less than 0.75. In cases where the Kel interval is not assigned, the values of t½, AUC0-inf, and AUC%extrap are considered not calculable and will not be reported. Wherever the resulting t½ is more than half as long as the sampling interval, the Kel values and associated

parameters (t½, AUC0-inf, and AUC%extrap) may not be presented as judged appropriate and in accordance with Celerion SOPs.

6.6 Data Summarization and Presentation

All LOXO-292 and moxifloxacin PK concentrations and PK parameters descriptive statistics will be generated using SAS® Version 9.3 or higher.

The plasma concentrations of LOXO-292 and moxifloxacin will be listed and summarized by treatment and time point for all subjects in the PK Population. Plasma concentrations of LOXO-292 and moxifloxacin will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration time points. Excluded subjects will be included in the concentration listings, but will be excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as "BLQ" in the concentration listings and footnoted accordingly.

Mean and individual concentration-time profiles will be presented on linear and semi-log scales. Linear mean plots will be presented with and without SD.

Plasma LOXO-292 and moxifloxacin PK parameters will be listed and summarized by treatment for all subjects in the PK Population. PK parameters will be reported to 3 significant figures for individual parameters, with the exception of Tmax and t½, which will be presented with 2 decimal places. Summary statistics (n, Mean, SD, CV%, SEM, minimum, median, maximum, geometric mean [Geom Mean] and geometric CV% [Geom CV%]) will be calculated for plasma LOXO-292 and moxifloxacin PK parameters. Excluded subjects will be listed in the PK parameter tables, but will be excluded from the summary statistics and noted as such in the tables.

The level of precision for each concentration and PK parameter statistic will be presented as follows:

- minimum/maximum in same precision as in bioanalytical data and parameter output,
- mean/median/Geom Mean in one more level of precision than minimum/maximum,
- SD/SEM in one more level of precision than mean/median/Geom Mean,
- n will be presented as an integer, and
- CV%/ Geom CV% will be presented to the nearest tenth.

No inferential statistics will be performed on PK concentrations or parameters.

7. SAFETY

No inferential statistics are to be performed for the safety analysis.

All clinical safety and tolerability data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination (ET), chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts will be reported for categorical data when appropriate.

The level of precision will be presented as follows: "n" as an integer, minimum/maximum in same precision as in the database, mean/median in one more precision level than minimum/maximum, and SD in one more precision level than mean/median.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

When change from baseline is calculated, baseline is the last scheduled assessment before dosing, including rechecks and unscheduled assessments, whichever is later, unless otherwise specified in the sections below. Rechecks, unscheduled assessments and ET measurements taken after dosing will not be used in the summarization.

7.1 Subject Discontinuation

Subjects will be summarized by the number of subjects enrolled, completed, and discontinued from the study with discontinuation reasons by randomized treatment sequence and overall. Discontinuation data will be listed by-subject.

7.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) for randomized treatment sequence and study overall. Weight, height and body mass index are summarized at screening. Age will be derived from the date of birth to the date of first dosing at Period 1. Frequency counts will be provided for categorical variables (race, ethnicity, and sex) for overall. A by-subject listing will also be provided.

7.3 Adverse Events

All AEs occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 22.0.

Each AE will be graded, by the clinical site, on the National Institution of Health's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) 5-point severity scale (Grade 1, 2, 3, 4 and 5). Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection.

The following clinical descriptions of severity for each AE are based on the following general guideline [CTCAE Nov2017]:

Table 7.3: Adverse Event Severity Level and Description

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.□	

Similarly, the causal relationship of the study drugs to the AE will be described as Related or Unrelated to study drugs LOXO-292 or moxifloxacin.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, treatment group, severity grade, relationship to study drugs, and action; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an undesirable event not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment. Each TEAE will be attributed to a treatment based on Investigator (or

designee) judgment as well as on its onset date and time. An AE that occurs during the washout period between treatments will be considered treatment-emergent to the last treatment given. If an AE has a change in severity grade, the original AE will be given a resolution date and time of the time of severity grade increase or decrease and a new AE record will be initiated with the new severity grade, and the new AE record will use the resolved date/time of the previous record as the onset date/time. If an AE decreases in severity grade, the new AE record with less severity will be considered and counted as the same AE event of the previous record with worse severity under the same treatment group and period in the analysis. If the severity grade of an AE remains the same, the AE will be kept open through to resolution.

If the onset time of an AE is missing and the onset date is the same as the treatment dosing date, then the AE will be considered treatment-emergent in both the prior and current treatment. If the onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment-emergent for the last treatment administered. If the onset date of an AE is missing, then the AE will be considered treatment-emergent and attributed to the first treatment group on the study, unless the onset date is known to have occurred within or between specific treatment periods.

TEAEs will be tabulated by system organ class and preferred term. Summary tables will include the number of subjects reporting the AE and as a percent of the number of subjects dosed by treatment and overall. Tables will also be presented by severity grade and relationship to study drugs. If a subject experienced the same TEAE at more than once with different level of severity grade for a given treatment, only the most severe one will be counted. Similarly, if a subject experienced the same TEAE at more than once with different level of drug relationship for a given treatment, only the one most closely related to each study drug will be counted.

Should any serious adverse events (SAEs) occur during the study, the SAEs will be displayed in a table and a narrative included in the CSR.

7.4 Clinical Laboratory Tests (Serum Chemistry, Hematology, Coagulation, and Urinalysis)

All clinical laboratory test results will be presented in by-subject data listings, however, only serum chemistry, hematology, coagulation and urinalysis values will be summarized.

Hematology, coagulation, serum chemistry and urinalysis tests will be conducted at the following time points:

Table 7.4 Lab Test Time Points

Period	Period Day
Screen	

1	Day -1 (check-in)
1-4	Day 3, Day 6, Day 11
End of Treatment/Early Termination	
Period Day 1 in Periods 2-4 is the same as Period Day 11 of the previous period.	

Out-of-normal range (OOR) flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a computer clinically significant (CS) range suggested by the PI (Celerion SOP GSOP.10.1028). If the value falls within the computer CS range, it will be noted as "N" for not clinically significant. If the value fails (i.e., falls outside of the CS range) the computer CS range, it will be flagged with a "Y" which prompts the PI to determine how the OOR value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. To distinguish the PI flag from the CS range flags, the PI flags "N" and "Y" will be presented as "-" and "+" in the data listings, respectively. Additionally, the PI will provide a 4th flag when the 3rd flag indicates "R" or "^". This 4th flag is intended to capture final CS (+)/NCS (-) when the 3rd flag does not document significance. In addition, CTCAE, version 5.0 grading (found in NCI CTCAE guidance) will be applied to all out of range lab values deemed clinically significant by the Investigator (or designee) which are recorded as AEs.

Out-of-range values and corresponding recheck results will be listed. Results that are indicated as CS by the PI (in either PI flag) will be listed in the table. Out-of-range values laboratory value results which are indicated as CS by PI will be reported as AEs.

For all laboratory values that are numeric, descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment and time point. Change from baseline will also be summarized. Postdose unscheduled events or rechecks will not be summarized. Similarly, ET results will not be included in summaries.

For each laboratory test, a shift table will be developed comparing the frequency of the results at baseline (above normal, normal, or below normal) to postdose results. For urinalysis tests, the categories are normal and outside normal.

Baseline is Day -1 of Period 1 and Day 11 of previous period for Periods 2, 3, 4 and is the last non-missing predose measurement prior to dosing, including rechecks and unscheduled assessments. Day 11 measurement of Periods 1, 2, 3 might be replicated as postdose value of Periods 1, 2, 3 and baseline value of Period 2, 3, 4. When serving as baseline of Periods 2, 3, 4, the recheck or unscheduled values after Day 11 of Periods 1, 2, 3 and prior to dosing of Periods 2, 3, 4 could be used as baseline.

7.5 Vital Signs (Blood Pressure, Pulse Rate, Respiration Rate, and Temperature)

Vital signs will be performed at the following time points:

Table 7.5 Vital Signs Time Points

Period	Period Day	Study Hour	Assessment*
Screen			HR, BP, RR, T
1	Day -1 (check-in)		HR, BP, RR, T
1-4	Day 1	-0.75	HR, BP, RR, T
1-4	Day 1	0.75, 2, 4	HR, BP, RR
1-4	Day 2	24, 36	HR, BP, RR
1-4	Day 3	48	HR, BP, RR
1-4	Day 4	72	HR, BP, RR
1-4	Day 5	96	HR, BP, RR
1-4	Day 6	120	HR, BP, RR
1-4	Day 11	240	HR, BP, RR, T
End of Treatment/Early Termination			HR, BP, RR, T
* HR = Heart Rate, BP = Blood Pressure, RR = Respiration Rate, T = Temperature Period Day 1 in Periods 2-4 is the same as Period Day 11 of the previous period.			

Descriptive statistics will be reported for vital sign measurements (blood pressure, pulse, and respiration rate) and change from baseline by treatment and time point. Baseline is Day 1 predose and is the last non-missing predose measurement prior to dosing, including rechecks and unscheduled assessments. Postdose rechecks, unscheduled assessments, and ET results will not be used for calculation of descriptive statistics. All vital signs results will be listed by subject.

7.6 Safety ECG (Heart Rate, PR, QRS, QT, and QTcF [QT with Fridericia correction])

Single 12-lead ECGs will be performed at the following time points:

Table 7.6: ECG Time Points

Period	Period Day	Study Hour
Screen	Screening	
1-4	Day 1	-0.75, 2, 4
1-4	Day 2	24, 36
1-4	Day 3	48

Period	Period Day	Study Hour
1-4	Day 4	72
1-4	Day 5	96
1-4	Day 6	120
1-4	Day 11	240
End of Treatment/Early Termination		
Period Day 1 in Periods 2-4 is the same as Period Day 11 of the previous period.		

Descriptive statistics will be reported for ECG parameters and change from baseline by treatment and time point. Baseline is Day 1 predose and is the last non-missing predose measurement prior to dosing, including rechecks and unscheduled assessments. Postdose rechecks, unscheduled assessments, and ET results will not be used for calculation of descriptive statistics. All ECG interval parameters will be listed by subject and time point of collection with QTcF > 450 msec and change from baseline > 30 msec flagged.

7.7 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary, Version 01-Mar-2019 b3 and listed.

7.8 Physical Examination

A full physical examination will be performed at screening. An abbreviated physical examination will be performed on Day 1 (prior to dosing of each period). Abnormal findings will be reported as medical history or adverse events by the clinical site. Physical examination results will be listed by subject and time point.

8. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol.

9. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Council for Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all summary tables and figures will be generated using SAS® Version 9.3 or higher.

9.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Table 10-1 Summary of Disposition (Safety Population)

Section 11:

Table 11-1 Demographic Summary (Safety Population)

Table 11-2 Summary of Plasma LOXO-292 Pharmacokinetic Parameters Following Administration of a Single Oral Dose of CCI mg LOXO-292 (Treatment A) and Single Oral Dose of CCI mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Table 11-3 Summary of Plasma Moxifloxacin Pharmacokinetic Parameters Following Administration of a Single Oral Dose of CCI mg Moxifloxacin (Treatment C) (Pharmacokinetic Population)

Figure 11-1 Arithmetic Mean Plasma LOXO-292 Concentration-Time Profiles Following Administration of a Single Oral Dose of CCI mg LOXO-292 (Treatment A) and Single Oral Dose of CCI mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Figure 11-2 Arithmetic Mean Plasma Moxifloxacin Concentration-Time Profile Following Administration of a Single Oral Dose of CCI mg Moxifloxacin (Treatment C) (Pharmacokinetic Population)

Section 12:

Table 12-1 Treatment-Emergent Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population)

9.2 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

14.1.1 Demographic Tables

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1 Serious Adverse Events (Safety Population)

<If no serious adverse event occurred, a statement 'There was no serious adverse event recorded during the study.' will be added.>

14.3.3. Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4. Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1 Out-of-Range Values and Recheck Results - Serum Chemistry (Safety Population)

Table 14.3.4.2 Out-of-Range Values and Recheck Results – Hematology and Coagulation

Table 14.3.4.3 Out-of-Range Values and Recheck Results – Urinalysis

Table 14.3.4.4 Clinically Significant Laboratory and Corresponding Results (Safety Population)

14.3.5. Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.1 Clinical Laboratory Summary and Change From Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.2 Clinical Laboratory Shift From Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.3 Clinical Laboratory Summary and Change From Baseline – Hematology and Coagulation (Safety Population)

Table 14.3.5.4 Clinical Laboratory Shift From Baseline – Hematology and Coagulation (Safety Population)

Table 14.3.5.5 Clinical Laboratory Summary and Change From Baseline – Urinalysis (Safety Population)

Table 14.3.5.6 Clinical Laboratory Shift From Baseline – Urinalysis (Safety Population)

Table 14.3.5.7 Vital Sign Summary and Change From Baseline (Safety Population)

Table 14.3.5.8 12-Lead Electrocardiogram Summary and Change From Baseline (Safety Population)

9.3 Section 16 Data Listings

Note: Virology test results (Hepatitis and HIV) that are provided by the clinical laboratory will not be presented in subject data listings and will not be included in the database transfer.

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

Appendix 16.1.9 Statistical Methods

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2. Subject Data Listings

16.2.1. Subject Discontinuation

Appendix 16.2.1 Subject Discontinuation (Safety Population)

16.2.2. Protocol Deviations

Appendix 16.2.2 Protocol Deviations

Note: Protocol deviations will be provided by the clinical study manager as Microsoft Excel file and read into the SDTM to generate the data listing.

16.2.3. Subjects Excluded from Pharmacokinetic Analysis

Appendix 16.2.3 Subjects Excluded from Pharmacokinetic Analysis

Note: Appendix 16.2.3 is generated in MS Word for inclusion in the CSR.

16.2.4 Demographic Data

Appendix 16.2.4.1 Demographics (Safety Population)
Appendix 16.2.4.2 Updated Informed Consent (Safety Population)
Appendix 16.2.4.3 Physical Examination (Safety Population)
Appendix 16.2.4.4 Medical and Surgical History (Safety Population)
Appendix 16.2.4.5 Nicotine Use (Safety Population)

16.2.5. Compliance and Drug Concentration Data

Appendix 16.2.5.1.1 Inclusion Criteria
Appendix 16.2.5.1.2 Exclusion Criteria
Appendix 16.2.5.2 Subject Eligibility (Safety Population)
Appendix 16.2.5.3.1 Check-in Criteria
Appendix 16.2.5.3.2 Check-in Responses (Safety Population)
Appendix 16.2.5.4.1 Test Compound Description

Appendix 16.2.8.5 Phone Call (Safety Population)

10. TABLE AND FIGURE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables and figures that will be presented and included in the final CSR. Unless otherwise noted, all in-text tables will be presented in Times New Roman font size 8 and post-text tables in Courier New size font 9. These tables will be generated according to the ADaM Model 2.1 and ADaM implementation guide 1.1.

Actual treatment sequence will be used unless the column header uses the reference randomized sequence. Period Day will be used unless there is a footnote describing that the day referenced is using Period 1 Day 1 (ie, AE listing).

10.1 In-text Table Shells

Table 10-1 Summary of Disposition (Safety Population)

Disposition	Randomized Sequence				Overall
	ABCD	BCDA	CDAB	DABC	
Enrolled	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)
Completed Study	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Discontinued Early	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
<Reason1>	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
<Reason2>	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Source: Table 14.1.1.1
Program: /CAXXXXX/sas_prg/stsas/intext/t_disp.sas DDMMMYYYY HH:MM

Table 11-1 Demographic Summary (Safety Population)

Trait		Randomized Sequence				Study Overall
		ABCD	BCDA	CDAB	DABC	
Sex	Male	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Female	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Race	Asian	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Black or African American	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	White	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Ethnicity	Hispanic or Latino	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Not Hispanic or Latino	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Age* (yr)	n	XX	XX	XX	XX	XX
	Mean	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
	SD	XX.XXX	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	Minimum	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
	Median	XX.X	XX.X	XX.X	XX.X	XX.X
	Maximum	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Height (cm)	n	XX	XX	XX	XX	XX
	Mean	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XXX	XXX	XXX	XXX	XXX
	Median	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X
	Maximum	XXX	XXX	XXX	XXX	XXX

* Age is calculated from the date of first dosing.
BMI = Body mass index

Source: Table 14.1.1.3
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: Weight (kg) and BMI (kg/m^2) will also be summarized in the table above.

In-text Tables 11-2 and 11-3 will be in the following format:

Table 11-2 Summary of Plasma LOXO-292 Pharmacokinetic Parameters Following Administration of a Single Oral Dose of CCI mg LOXO-292 (Treatment A) and Single Oral Dose of CCI mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Pharmacokinetic Parameters	CCI mg LOXO-292	CCI mg LOXO-292
Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param4 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]

CCI mg LOXO-292: CCI mg LOXO-292 (CCI CCI mg CCI) and LOXO-292 matching placebo CCI CCI mg matching placebo CCI) administered at Hour 0 on Day 1
CCI mg LOXO-292: CCI mg LOXO-292 (CCI CCI mg CCI) administered at Hour 0 on Day 1

AUC and Cmax values are presented as geometric mean (geometric CV%).
Tmax values are presented as median (min, max).
Other parameters are presented as arithmetic mean (± SD).
Source: Tables 14.2.1.1.4 and 14.2.1.1.5

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, and t½;
- Table 11-2 source: Tables 14.2.1.1.4 and 14.2.1.1.5
- Table 11-3 source: Table 14.2.2.1.2
- n will be presented as an integer (with no decimal);
- Summary statistics will be presented with same precision as defined in post-text shells

```
Program:  /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas        DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas     DDMMMYYYY  HH:MM
```

Table 12-1 Treatment-Emergent Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population)

Adverse Events*	Treatment				Overall
	A	B	C	D	
Number of Subjects Dosed	XX (100%)	XX (100%)	XX (100%)	Similar to Previous Column	XX (100%)
Number of Subjects With TEAEs	XX (XX%)	XX (XX%)	XX (XX%)		XX (XX%)
Number of Subjects Without TEAEs	XX (XX%)	XX (XX%)	XX (XX%)		XX (XX%)
System Organ Class 1	X (X%)	X (X%)	X (X%)		X (X%)
Preferred Term 1	X (X%)	X (X%)	X (X%)		X (X%)
Preferred Term 2	X (X%)	X (X%)	X (X%)		X (X%)
System Organ Class 2	X (X%)	X (X%)	X (X%)		X (X%)
Preferred Term 1	X (X%)	X (X%)	X (X%)		X (X%)
Preferred Term 2	X (X%)	X (X%)	X (X%)		X (X%)

* Adverse events are coded using MedDRA® Version 22.0 by System Organ Class and Preferred Term.
TEAE = Treatment-emergent Adverse event
Although a subject may have had 2 or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
If a TEAE decreased in severity grade, the new TEAE record with less severity was counted as the same TEAE event of the previous record with worse severity under the same treatment group.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

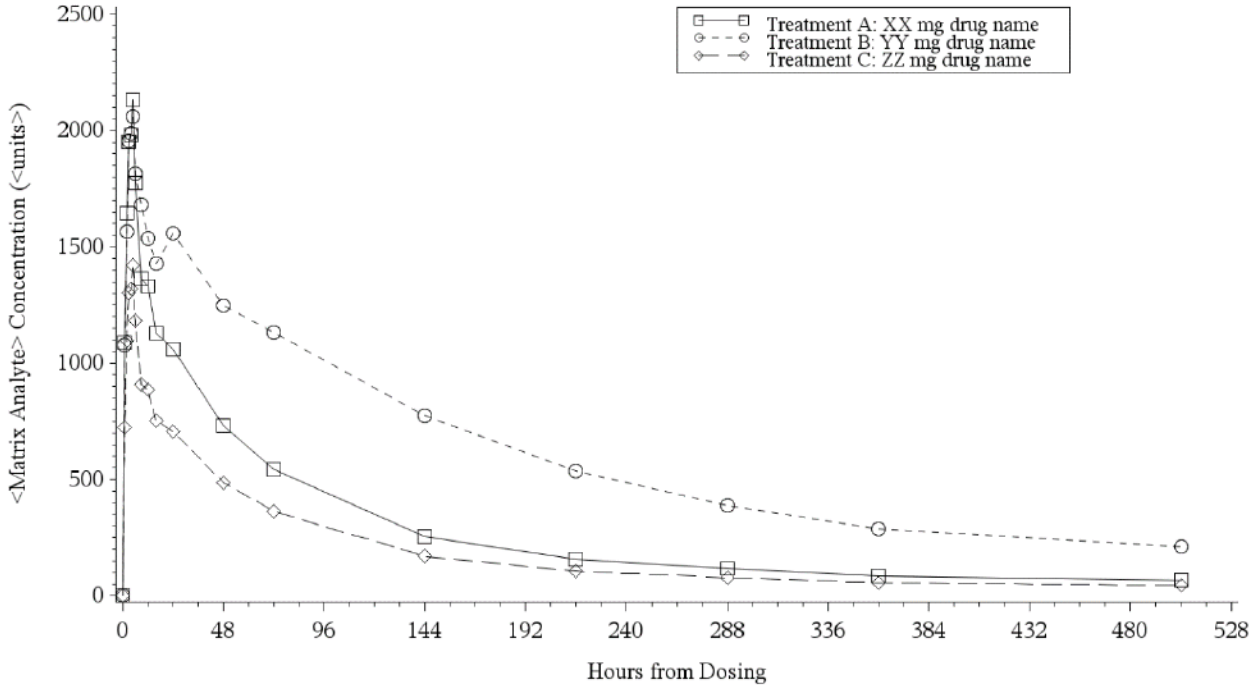
Source: Table 14.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_ae.sas DDMMMYYYY HH:MM

Programmer Note: Sort by decreasing frequency of system organ class and by preferred term within a system organ class of Overall column.

10.2 Figures Shells

In-text Figures 11-1 and 11-2 and Figures 14.2.1.2.2 and 14.2.2.2.2 will be in the following format:

Figure 11-1 Arithmetic Mean Plasma LOXO-292 Concentration-Time Profiles Following Administration of a Single Oral Dose of CCI mg LOXO 292 (Treatment A) and Single Oral Dose of CCI mg LOXO-292 (Treatment B) (Pharmacokinetic Population)



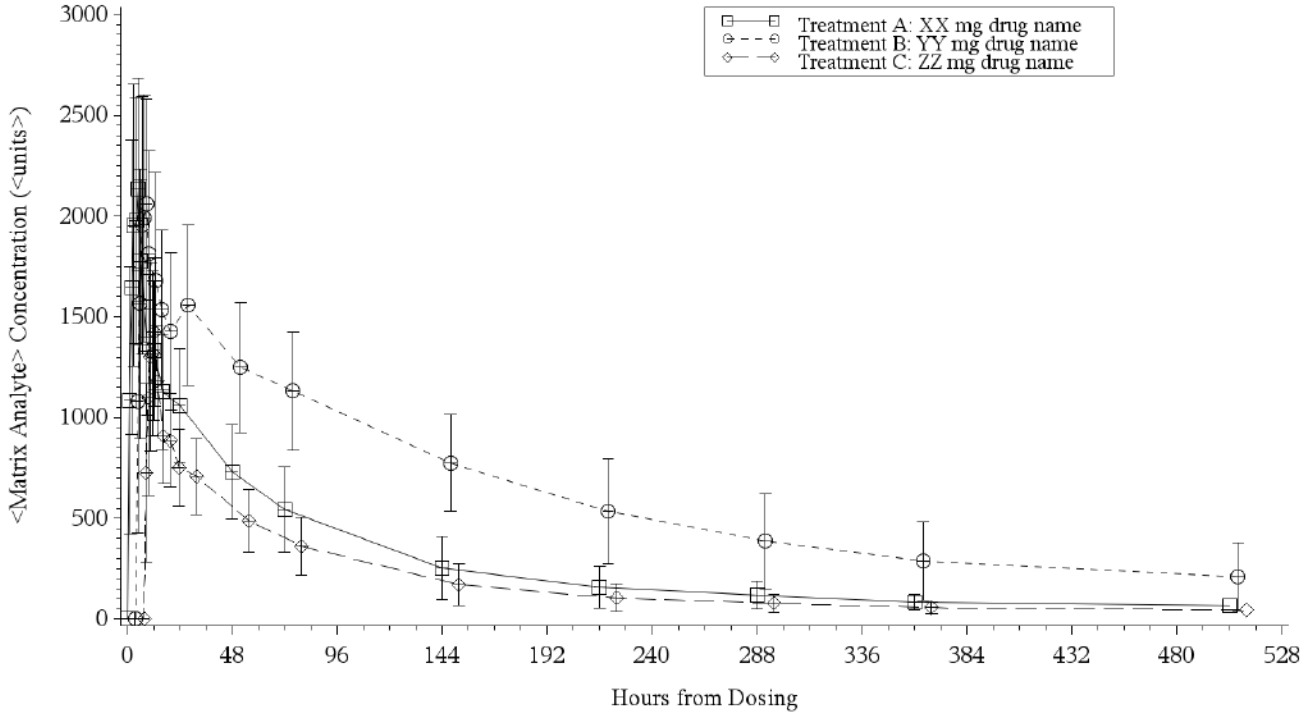
Notes for Generating the Actual Mean Figure:

- Figures 11-1 and 14.2.1.2.2:
  - Legend will be:
    - Treatment A: CCI mg LOXO-292
    - Treatment B: CCI mg LOXO-292
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Dose"
  - Add in footnote: LLOQ value for LOXO-292 is 1.00 ng/mL
- Figures 11-2 and 14.2.2.2.2:
  - Legend will be:
    - CCI mg moxifloxacin
  - Y-axis label will be "Plasma Moxifloxacin Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Moxifloxacin Dose"
  - Add in footnote: LLOQ value for moxifloxacin is 25 ng/mL.

```
Program:  /CAXXXXX/sas_prg/pksas/meangraph.sas         DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_meangraph.sas       DDMMMYYYY  HH:MM
```

Figures 14.2.1.2.1 and 14.2.2.2.1 will be in the following format:

Figure 14.2.1.2.1 Arithmetic Mean (SD) Plasma LOXO-292 Concentration-Time Profiles Following Administration of a Single Oral Dose of CCI mg LOXO 292 (Treatment A) and Single Oral Dose of CCI mg LOXO-292 (Treatment B) (Pharmacokinetic Population)



Treatments B and C are shifted to the right for ease of reading
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYY HH:MM

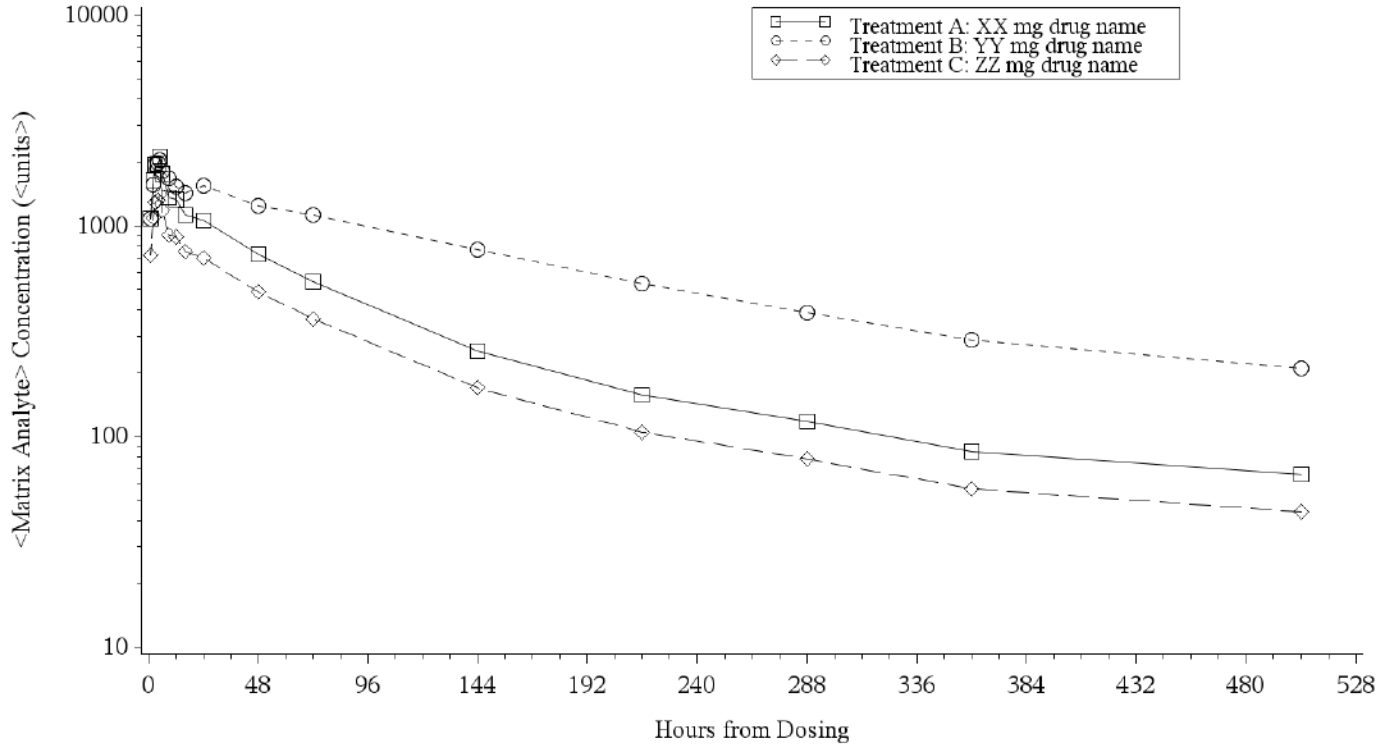
Notes for Generating the Actual Mean Figure:

- Figures 14.2.1.2.1:
  - Legend will be:
    - Treatment A: CCI mg LOXO-292
    - Treatment B: CCI mg LOXO-292
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Dose"
  - Add in footnote: LLOQ value for LOXO-292 is 1.00 ng/mL
- Figures 14.2.2.2.1:
  - Legend will be:
    - CCI mg moxifloxacin
  - Y-axis label will be "Plasma Moxifloxacin Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Moxifloxacin Dose"
  - Add in footnote: LLOQ value for moxifloxacin is 25 ng/mL.

```
Program:  /CAXXXXX/sas_prg/pksas/meangraph.sas         DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_meangraph.sas       DDMMMYYYY  HH:MM
```

Figures 14.2.1.2.3 and 14.2.2.2.3 will be in the following format:

Figure 14.2.1.2.3 Mean Plasma LOXO-292 Concentration-Time Profiles Following Administration of a Single Oral Dose of CCI mg LOXO-292 (Treatment A) and Single Oral Dose of CCI mg LOXO-292 (Treatment B) (Semi-Log Scale) (Pharmacokinetic Population)



Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYY HH:MM

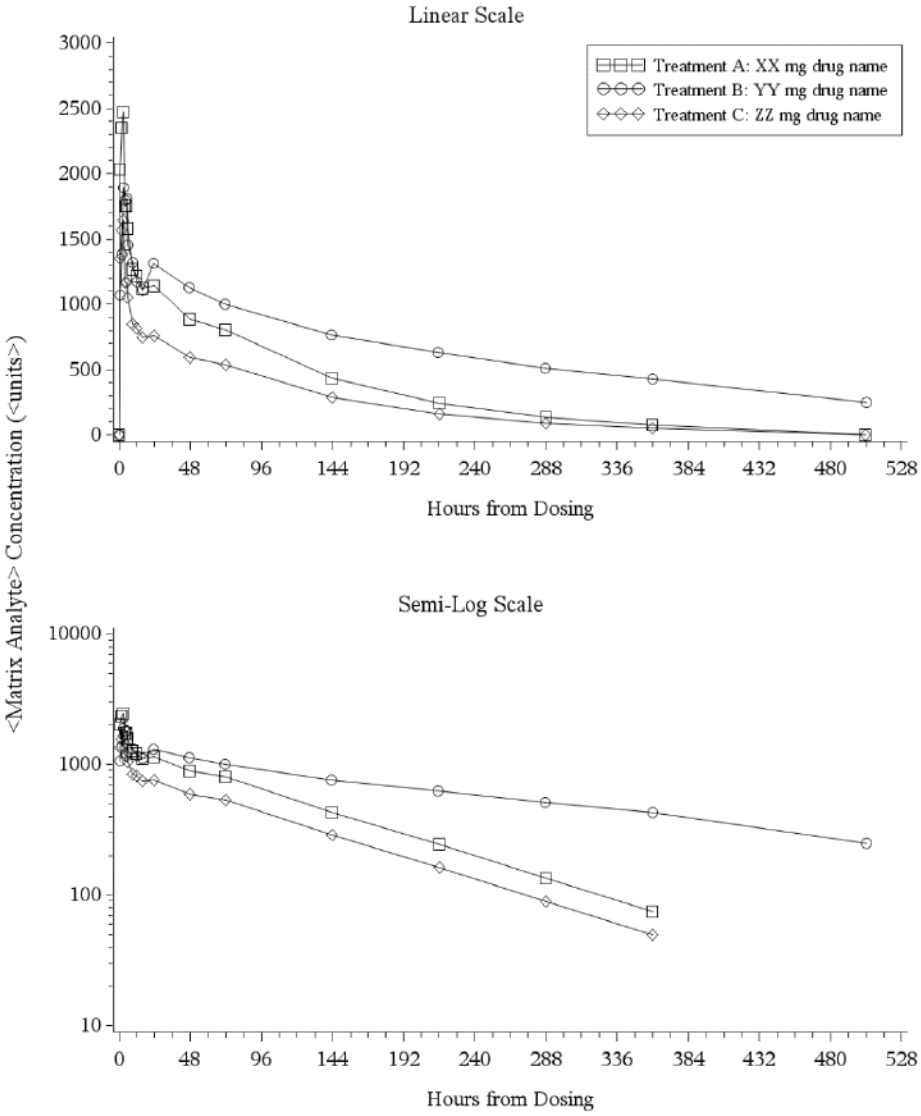
Notes for Generating the Actual Mean Figure:

- Figures 14.2.1.2.3:
  - Legend will be:
    - Treatment A: CCI mg LOXO-292
    - Treatment B: CCI mg LOXO-292
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Dose"
  - Add in footnote: LLOQ value for LOXO-292 is 1.00 ng/mL
- Figures 14.2.2.2.3:
  - Legend will be:
    - CCI moxifloxacin
  - Y-axis label will be "Plasma Moxifloxacin Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Moxifloxacin Dose"
  - Add in footnote: LLOQ value for moxifloxacin is 25 ng/mL.

```
Program:  /CAXXXXX/sas_prg/pksas/meangraph.sas         DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_meangraph.sas       DDMMMYYYY  HH:MM
```

Appendix 16.2.6.1 and 16.2.6.2 will be in the following format:

Appendix 16.2.6.1
Individual Plasma LOXO-292 Concentration Versus Time Profiles Following Administration of a Single Oral Dose of CCI mg LOXO-292 (Treatment A) and Single Oral Dose of CCI mg LOXO-292 (Treatment B) for Subject X (Linear and Semi-Log Scales)



Program: /CAXXXXX/sas_prg/pksas/adam_indgraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/indgraph-all.sas DDMMMYYY HH:MM

Notes for Generating the Actual Individual Figure:

- Appendix 16.2.6.1:
  - Legend will be:
    - Treatment A: CCI mg LOXO-292
    - Treatment B: CCI mg LOXO-292
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Dose"
  - Add in footnote: LLOQ value for LOXO-292 is 1.00 ng/mL
- Appendix 16.2.6.2:
  - Legend will be:
    - CCI mg moxifloxacin
  - Y-axis label will be "Plasma Moxifloxacin Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Moxifloxacin Dose"
  - Add in footnote: LLOQ value for moxifloxacin is 25 ng/mL.

```
Program:  /CAXXXXX/sas_prg/pksas/indgraph-all.sas        DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_indgraph.sas       DDMMMYYYY  HH:MM
```

10.3 Post-text Table Shells

Page X of X

Table 14.1.1.1 Summary of Disposition (Safety Population)

	Randomized Sequence				
Disposition	ABCD	BCDA	CDAB	DABC	Overall
Enrolled	XX	XX	XX	XX	XX
Completed	XX	XX	XX	XX	XX
Discontinued Early	XX	XX	XX	XX	XX
Reason 1	XX	XX	XX	XX	XX
Reason 2	XX	XX	XX	XX	XX
Reason 3	XX	XX	XX	XX	XX
etc.					

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.1.1.2 Disposition of Subjects (Safety Population)

Subject Number	Randomized Sequence	Dosed Period 1	2	3	4	Study Completion Status	Date
XXX-XXX	XXXX	Yes	Yes	Yes	Yes	Completed Study	DDMMYYYY
XXX-XXX	XXXX	Yes	Yes	Yes	No	Terminated Study Prematurely	DDMMYYYY

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.1.1.3 Demographic Summary (Safety Population)

Trait		Randomized Sequence ABCD	BCDA	CDAB	DABC	Study Overall
Sex	Male	X (XX%)	<similar to column ABCD for all other columns>			
	Female	X (XX%)				
Race	Asian	X (XX%)				
	Black or African American	X (XX%)				
	White	X (XX%)				
Ethnicity	Hispanic or Latino	X (XX%)				
	Not Hispanic or Latino	X (XX%)				
Age*(yr)	n	XX				
	Mean	XX.X				
	SD	X.XX				
	Minimum	XX				
	Median	XX.X				
	Maximum	XX				
Height (cm)	n	XX				
	Mean	XX.X				
	SD	X.XX				
	Minimum	XX				
	Median	XX.X				
	Maximum	XX				

Programmer Note: Also include weight (kg) and BMI (kg/m^2)

Note: * Age is calculated from the date of first dosing.
BMI = Body mass index

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.1.3, and 14.2.2.1.1 will be in the following format:

Table 14.2.1.1.1 Plasma LOXO-292 Concentrations (ng/mL) Following Administration of a Single Oral Dose of CCI mg LOXO-292 (Treatment A)
(Pharmacokinetic Population)

			Sample Times (hr)								
Subject Number	Treatment Sequence	Study Period	Predose	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
n			XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SD			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%			.	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum			XX	XX	XX	XX	XX	XX	XX	XX	XX
Median			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Maximum			XX	XX	XX	XX	XX	XX	XX	XX	XX

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 1 ng/mL are treated as 0 before the first quantifiable concentration and as missing elsewhere.
. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- Present the subject number in the following format: XXX-XXX
- Concentrations will be presented to same precision as in the bioanalytical data.
- Summary statistics presentation with respect to the precision of the bioanalytical data: n = integer; Mean and Median +1; SD and SEM +2, Min and Max +0, CV% to 1 decimal

Programmer Note:

- PK Time points are:
    - LOXO-292 Tables 14.2.1.1.1, 14.2.1.1.2, and 14.2.1.1.3: predose and 0.25, 0.5, 0.75, 1.5, 2, 2.5, 3, 4, 7, 9, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose.
    - Moxifloxacin Table 14.2.2.1.1: predose and 0.25, 0.5, 0.75, 1.5, 2, 2.5, 3, 4, 7, 9, 12, and 24 hours postdose.

```
Program:  /CAXXXXX/sas_prg/pksas/pk-conc-tables.sas            DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/pk-conc-tables-sig.sas        DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_conc.sas                 DDMMMYYYY  HH:MM
```

Tables 14.2.1.1.4, 14.2.1.1.5 and 14.2.2.1.2 will be in the following format:

Table 14.2.1.1.4 Plasma LOXO-292 Pharmacokinetic Parameters Following Administration of a Single Oral Dose of [redacted] mg LOXO-292 (Treatment A)
(Pharmacokinetic Population)

			Parameters					
Subject Number	Treatment Sequence	Study Period	param1 (units)	param2 (units)	param3 (units)	param4 (units)	param5 (units)	param6 (units)
XXX-XXX	XXXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXXX	X	X.XX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
n			XX	XX	XX	XX	XX	XX
Mean			XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
SD			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum			XX.X	X.XX	XXX	XXX	XX.X	X.XXX
Median			XX.XX	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Maximum			XXX	X.XX	XXX	XXX	XX.X	X.XXX
Geom Mean			XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Geom CV%			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- Present the subject number in the following format: XXX-XXX;
- The following PK parameters will be presented in the following order: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, and t½;
- n will be presented as an integer (with no decimal);
- Parameter values for exposure-based parameters (i.e. AUCs, AUC%extrap, and Cmax) will be presented with 3 significant figures.
    - Summary statistics for exposure parameters will be presented as: Mean, Median, and Geom Mean +1; SD and SEM +2, Min and Max +0 with respect to the number of significant figures.
- Values for time-based parameters (i.e. Tmax, and t½) will be presented with 2 decimals.
    - Summary statistics for time-based parameters will be presented as: Mean, Median, and Geom Mean +1; SD and SEM +2, Min and Max +0 with respect to the number of decimals.
- Values for rate constants (i.e. Kel) will be presented with 3 significant figures.
    - Summary statistics for Kel will be presented as: Mean, Median, and Geom Mean +1; SD and SEM +2, Min and Max +0 with respect to the number of significant figures.
- CV% and Geom CV% for all parameters will be presented with 1 decimal
- Table 14.2.1.1.4, 14.2.1.1.5 will be for LOXO-292 and Table 14.2.2.1.2 will be for moxifloxacin

```
Program:  /CAXXXXX/sas_prg/pksas/pk-tables.sas          DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_pkparam.sas       DDMMMYYYY  HH:MM
```

Tables 14.2.1.1.6 and 14.2.2.1.3 will be in the following format:

Table 14.2.1.1.6 Intervals (Hours) Used for Determination of Plasma LOXO-292 Kel Values Following Administration of a Single Oral Dose of [redacted] mg LOXO-292 (Treatment A) and Single Oral Dose of [redacted] mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Subject Number	Treatment Sequence	Treatment A			Treatment B		
		Interval	R2	n	Interval	R2	n
XXX-XXX	XXXX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
XXX-XXX	XXXX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
XXX-XXX	XXXX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
XXX-XXX	XXXX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
XXX-XXX	XXXX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
XXX-XXX	XXXX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X

Treatment A: [redacted] mg LOXO-292 ([redacted] mg [redacted]) and LOXO-292 matching placebo ([redacted] [redacted] mg matching placebo [redacted]) administered at Hour 0 on Day 1
Treatment B: [redacted] mg LOXO-292 ([redacted] [redacted] mg [redacted]) administered at Hour 0 on Day 1

R2 = Coefficient of determination
n = Number of points used in Kel calculation
. = Kel value not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- Present the subject number in the following format: XXX-XXX
- Interval start and stop times will be presented to 1 decimal or 3 significant figures minimum;
- R2 will be presented to 3 decimals;
- n will be presented as an integer (with no decimal)

Program: /CAXXXXX/sas_prg/pksas/kel-tables-xover.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_kel.sas DDMMMYYYY HH:MM

Table 14.3.1.1 Treatment-Emergent Adverse Event Frequency by Treatment - Number of Subjects Reporting Events (% of Subject Dosed) (Safety Population)

	Treatment				
TE Adverse Event*	A	B	C	D	Overall
Number of Subjects Dosed	X (100%)	X (100%)	X(100%)	X(100%)	<similar to
Number of Subjects with TE Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)	previous columns>
Number of Subjects without TE Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Nervous system disorders	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Dizziness	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Headache	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Presyncope	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Respiratory, thoracic and mediastinal disorders	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Dry throat	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Oropharyngeal pain	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Sinus congestion	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Sneezing	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
General disorders and administration site conditions	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Fatigue	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
Thirst	X (XX%)	X (XX%)	X (XX%)	X (XX%)	
etc.					

Note: * Adverse events are classified according to the MedDRA Version 22.0 by System Organ Class and Preferred Term.
TE = Treatment-emergent
If a TEAE decreased in severity grade, the new TEAE record with less severity was counted as the same TEAE event of the previous record with worse severity under the same treatment group.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Sort by decreasing frequency of system organ class and by preferred term within a system organ class of Overall column. For each subject, please sort the AEs with same verbatim and preferred term by onset date/time. For any pair (e.g., AE_S1, AE_S2) of these AEs (for same subject, same verbatim and preferred term), if the onset date/time of AE_S2 = resolved date/time of AE_S1 and the grade of AE_S2 < the grade level of AE_S1, then mark the AE_S2 with a flag like EVAUL_FLG =”N”. Then, for AE analysis (summary tables), please exclude the ones with EVAUL_FLG =”N”. Won’t repeat this comment again.

Table 14.3.1.2 Treatment-Emergent Adverse Event Frequency by Treatment, Severity Grade, and Relationship to Study Drugs - Number of Subjects Reporting Events (Safety Population)

TE Adverse Event*	Treat-ment	Number of Subjects with Adverse Events	Severity Grade					Relationship to LOXO-292		Relationship to Moxifloxacin	
			1	2	3	4	5	Related	Not Related	Related	Not Related
Dizziness	A	X	X	X	X	X	X	X	X	X	X
Dry eye	B	X	X	X	X	X	X	X	X	X	X
Dry mouth	A	X	X	X	X	X	X	X	X	X	X
	C	X	X	X	X	X	X	X	X	X	X
Dry throat	D	X	X	X	X	X	X	X	X	X	X
Ear pain	A	X	X	X	X	X	X	X	X	X	X
Fatigue	D	X	X	X	X	X	X	X	X	X	X
Treatment A		XX	X	X	X	X	X	X	X	X	X
Treatment B		XX	X	X	X	X	X	X	X	X	X
Treatment C		XX	X	X	X	X	X	X	X	X	X
Treatment D		XX	X	X	X	X	X	X	X	X	X
Overall		XX	X	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 22.0 by System Organ Class and Preferred Term.
TE = Treatment-emergent; AE = Adverse event
Severity Grade: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to AE
Not all grades are appropriate for all AEs, therefore some AEs are listed in the CTCAE with fewer than 5 options for grade selection.
If a TEAE decreased in severity grade, the new TEAE record with less severity was counted as the same TEAE event of the previous record with worse severity under the same treatment group.
When a subject experienced the same TEAE at more than one level of severity during a treatment period, only the most severe one was counted.
When a subject experienced the same TEAE at more than one level of drug relationship during a treatment period, only the one related to study drugs was counted.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.2.1 Serious Adverse Events (Safety Population)

Subject Number	Treatment	TE?^	Adverse Event	PT*/ SOC	Onset/Resolution Day	Onset/Resolution Date	Onset/Resolution Time	Freq!	Severity Grade	Act~	Ser@	Outcome	Action for LOXO-292/ Moxifloxacin	Relationship to LOXO-292/ Moxifloxacin
XXX-XXX	X	Yes	XXXXXXX	XXXXXXX/ XXXXXXXX	XX/ XX	DDMMMYYYY/ DDMMMYYYY	XX:XX/ XX:XX	Inter.	X	X	NS	Resolved	XXXXXXXXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXXX

Note: * Adverse events are classified according to MedDRA Version 22.0 by System Organ Class and Preferred Term.
TE^ = Treatment-emergent; PT = Preferred Term; SOC = System Organ Class, Onset day is relative to Period 1 Day 1.
Freq! represents Frequency: SI = Single Episode, Inter. = Intermittent, Cont. = Continuous
Act~: 1 = None, 2 = Medication Required, 3 = Non-drug therapy required, 4 = Medication and Non-drug therapy required, 5 = Subject Withdrawn, 6 = Hospitalization, 7 = Other
Ser@ represents Serious: NS = Not Serious
Severity/Intensity: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to AE
Not all grades are appropriate for all AEs, therefore some AEs are listed in the CTCAE with fewer than 5 options for grade selection.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: if there are no serious adverse events reported, there will be just one table (Table 14.3.2.1) with the statement "There was no serious adverse event recorded during the study."

Tables 14.3.4.2-14.3.4.3 will have the following format.

Table 14.3.4.1 Out-of-Range Values and Recheck Results - Serum Chemistry (Safety Population)

Subject Number	Age$/ Sex	Study Period	Day	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)
XXX-XXX	XX/M	Screen		DDMMMYYYY	XX HN				XX HN
		1	-X	DDMMMYYYY		XX LN	XX HYR-		
		2	X	DDMMMYYYY				XX HN^+	
			X	DDMMMYYYY	XX LY-				
			X	DDMMMYYYY		XX LY-			

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early term chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for. Arrange alphabetically by lab test name.

Note: $ Age is calculated from the date of first dosing
Abnormal flag: H = Above Reference Range, L = Below Reference Range
Computer Clinical significance: N = Not Clinically Significant, Y = Clinically Significant
PI Interpretation: - = Not Clinically Significant, + = Clinically Signficant, R = To be Rechecked, ^ = Will be Retested at a Later Event

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.4.4 Clinically Significant Laboratory and Corresponding Results (Safety Population)

Subject Number	Age$/ Sex	Study Period	Day	Date	Time	Department	Test	Result		Reference Range	Unit
XXX-XXX	XX/X	X	X	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX		X - X	mg/dL
			X	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX	HYR+	X - X	mg/dL
			X	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX	HY-	X - X	mg/dL
			X	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX	HN	X - X	mg/dL

Programmer Note: All time points for a subject/test with at least one value deemed as CS by the PI will be presented in this table. If there were no CS values as deemed by PI (i.e., no "CS" or "Clinically Significant" in the PI flag [3rd or 4th field] in the laboratory dataset), then this table will contain only the statement: "There were no laboratory values deemed clinically significant by the PI in the study."

Note: $ Age is calculated from the date of first dosing
H = Above Reference Range, L = Below Reference Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI Interpretation: - = Not Clinically Significant, R = To be Rechecked, ^ = Will be Retested at a Later Event, + = Clinically Significant

Program : /CAXXXXX/ECR/sas_prg/stsas/tab/PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.5.1, 14.3.5.3, and 14.3.5.5 will have the following format.

Page 1 of X

Table 14.3.5.1 Clinical Laboratory Summary and Change from Baseline – Serum Chemistry (Safety Population)

				Treatment				Change From Baseline			
Laboratory Test (unit)	Normal Range#	Time Point	Statistic	A	B	C	D	A	B	C	D
Parameter1 (unit)	XX – XX	Baseline*	n	XX	XX	<similar to previous columns>		<populated for all except baseline>			
			Mean	XX.XX	XX.XX						
			SD	X.XXX	X.XXX						
			Minimum	XX.X	XX.X						
			Median	XX.XX	XX.XX						
			Maximum	XX.X	XX.X						
		Day 3	n	XX	XX						
			Mean	XX.XX	XX.XX						
			SD	X.XXX	X.XXX						
			Minimum	XX.X	XX.X						
			Median	XX.XX	XX.XX						
			Maximum	XX.X	XX.X						
		Day 6	n	XX	XX						
			Mean	XX.XX	XX.XX						
			SD	X.XXX	X.XXX						
			Minimum	XX.X	XX.X						
			Median	XX.XX	XX.XX						
			Maximum	XX.X	XX.X						

<Programmer note: Similar for remaining laboratory tests and time point. Sort alphabetically by lab test name.>

Note: # Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1 for the breakdown.
Baseline* is Day –1 of Period 1 and Day 11 of previous period for Periods 2, 3, 4 and is the last non-missing predose measurement prior to dosing, including rechecks and unscheduled assessments. Day 11 measurement of Periods 1, 2, 3 was replicated as postdose value of Periods 1, 2, 3 and baseline value of Periods 2, 3, 4.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.5.2, 14.3.5.4, and 14.3.5.6 will have the following format.

Page 1 of X

Table 14.3.5.2 Clinical Laboratory Shift from Baseline – Serum Chemistry (Safety Population)

Laboratory Test (units)	Treatment	Time Point	Baseline L: Postdose L	Baseline L: Postdose N	Baseline L: Postdose H	Baseline N: Postdose L	Baseline N: Postdose N	Baseline N: Postdose H	Baseline H: Postdose L	Baseline H: Postdose N	Baseline H: Postdose H
Testname(unit)	A	Day 3	X	XX	X	X	XX	X	X	XX	X
		Day 6	X	XX	X	X	XX	X	X	XX	X
		Day 11	X	XX	X	X	XX	X	X	XX	X
	B	Day 3	X	XX	X	X	XX	X	X	XX	X
		Day 6	X	XX	X	X	XX	X	X	XX	X
		Day 11	X	XX	X	X	XX	X	X	XX	X

<Programmer note: Similar for remaining treatments and laboratory tests. Use N = Within Normal Range, O = Outside Normal Range for urinalysis shift table.>

Note: N = Within Normal Range, L = Below Normal Range, H= Above Normal Range.
Baseline is Day -1 of Period 1 and Day 11 of previous period for Periods 2, 3, 4 and is the last non-missing predose measurement prior to dosing, including rechecks and unscheduled assessments. Day 11 measurement of Periods 1, 2, 3 was replicated as postdose value of Periods 1, 2, 3 and baseline value of Periods 2, 3, 4.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_programname.sas DDMMMYYYY HH:MM

Table 14.3.5.7 Vital Sign Summary and Change From Baseline (Safety Population)

Vital Sign Parameter (unit)	Time Point	Statistic	Treatment A	Treatment B	Treatment C	Treatment D	Change From Baseline A	Change From Baseline B	Change From Baseline C	Change From Baseline D
Parameter1 (unit)	Baseline*	n	XX	XX	XX	XX				
		Mean	XX.XX	XX.XX	XX.XX	XX.XX				
		SD	X.XXX	X.XXX	X.XXX	X.XXX				
		Minimum	XX.X	XX.X	XX.X	XX.X				
		Median	XX.XX	XX.XX	XX.XX	XX.XX				
		Maximum	XX.X	XX.X	XX.X	XX.X				
	Hour 0.75	n	XX	XX	XX	XX	XX	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Hour 2	n	XX	XX	XX	XX	XX	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

<Programmer note: Similar for remaining vital sign time points and parameters>

Note: Baseline* is the last non-missing predose measurement prior to dosing, including rechecks and unscheduled assessments.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.8 12-Lead Electrocardiogram Summary and Change from Baseline (Safety Population)

ECG Parameter (unit)	Time Point	Statistic	Treatment A	Treatment B	Treatment C	Treatment D	Change From Baseline A	Change From Baseline B	Change From Baseline C	Change From Baseline D
Parameter1 (unit)	Baseline	n	XX	XX	XX	XX				
		Mean	XX.XX	XX.XX	XX.XX	XX.XX				
		SD	X.XXX	X.XXX	X.XXX	X.XXX				
		Minimum	XX.X	XX.X	XX.X	XX.X				
		Median	XX.XX	XX.XX	XX.XX	XX.XX				
		Maximum	XX.X	XX.X	XX.X	XX.X				
	Hour 2	n	XX	XX	XX	XX	XX	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Hour 4	n	XX	XX	XX	XX	XX	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

<Programmer note: Similar for remaining time points and parameters.>

Note: Baseline* is the last non-missing predose measurement prior to dosing, including rechecks and unscheduled assessments.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

11. LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final CSR. These listings will be generated off of the Celerion SDTM Tabulation Model 1.4 mapped in accordance with SDTM Implementation Guide 3.2. All listings will be presented in Courier New size font 9.

Actual treatment sequence will be used unless the column header uses the reference randomized sequence. Period Day will be used unless there is a footnote describing that the day referenced is using Period 1 Day 1 (ie, AE listing).

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Reference Range	Unit
Serum Chemistry	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
Hematology	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units

<Programmer note: Sort alphabetically by lab test name within each lab group.>

<similar for remaining Laboratory Groups and Test Names>

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.1 Subject Discontinuation (Safety Population)

Subject Number	Randomized Treatment Sequence	Actual Treatment Sequence	Study Period	Date	Completed Study?	Primary Discontinuation Reason
XXX-XXX	XXXX	XXXX	Post	DDMMMYYYY	YES	<Programming Note: Include Specify after :>
XXX-XXX	XXXX	XXXX	Post	DDMMMYYYY	YES	
XXX-XXX	XXXX	XXXX	Post	DDMMMYYYY	YES	
XXX-XXX	XXXX	XXXX	Post	DDMMMYYYY	YES	
XXX-XXX	XXXX	XX__	Post	DDMMMYYYY	NO	Adverse Event
XXX-XXX	XXXX	XXXX	Post	DDMMMYYYY	YES	

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.2 Protocol Deviations (Safety Population)

Subject Number	Study Period	Treat-ment	Date	Day	Assessment	Deviation Type	SOP or Protocol Deviation	Deviation	Deviation Category	Action Taken
001-001	X	X	23FEB2019	X	OTHER: SOURCE DOCUMENTATION	STUDY ASSESSMENTS/ PROCEDURES	CELERION SOP GSOP.03.0011	THE STUDY SPECIFIC "DOSING COMPLIANCE" OVERLAY (SOURCE DOCUMENTATION UTILIZED TO DOCUMENT THAT THE SUBJECT WAS INSTRUCTED NOT TO CRUSH, SPLIT, OR CHEW THE STUDY DRUG PER PROTOCOL AND THAT SUBJECTS' HANDS WERE VERIFIED TO ENSURE THAT THE STUDY DRUGS WERE INGESTED) WAS NOT COMPLETED AT THE 168.00 HOUR TIMEPOINT.	MINOR	NO ACTION/ FOLLOW-UP REQUIRED
			25FEB2019	X	8 HOUR POST DOSE PK SAMPLE	LABORATORY ASSESSMENTS/ PROCEDURE	CELERION SOP GSOP.03.0040	BLOOD COLLECTION CONDITIONS OVERLAY (SOURCE DOCUMENTATION USED BY THE COLLECTION ASSOCIATE TO DOCUMENT THAT SAMPLES WERE HANDLED ACCORDING TO THE SPECIFICATION SHEET [SOURCE DOCUMENT CONTAINING DETAILED INSTRUCTIONS FOR STUDY PROCEDURES BASED ON THE PROTOCOL]) WAS NOT COMPLETED IN ERROR.	MINOR	NO ACTION/ FOLLOW-UP REQUIRED

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CA26434/sas_prg/stsas/lis/SDTM-LIS-DV.SAS 15MAY2019 11:29

Appendix 16.2.4.1 Demographics (Safety Population)

Subject Number	Date of Birth	Age* (yrs)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	Informed Consent Date	Informed Consent Version Date
XXX-XXX	DDMMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY	DDMMMYYYY

Note: * Age is calculated form the date of first dosing.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2 Updated Informed Consent (Safety Population)

Subject Number	Date Subject Signed Informed Re-Consent	Informed Re-Consent Version Date	Reason for Re-Consent
XXX-XXX	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXX
XXX-XXX	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXX
XXX-XXX	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXX
XXX-XXX	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXX
XXX-XXX	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXX
XXX-XXX	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXX
XXX-XXX	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXX

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.3 Physical Examination (Safety Population)

Subject Number	Treatment Sequence	Period	Day Hour	Date	Body System	Answer or Result	Comment
XXX-XXX	AB__	Screen		DDMMMYYYY	Was PE performed?	Yes	
					General	Normal	
					HEENT	Normal	
					< >	< >	
		1	1 -0.75	DDMMMYYYY	Was PE performed?	Yes	
					HEENT	Unchanged	
					< >	< >	

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.4 Medical and Surgical History (Safety Population)

Subject Number	Any History?	Study Period	Category	Body system	Date		Ongoing?	Condition or Events
					Start	End		
XXX-XXX	XXX	Screen	Medical	XXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	YES	XXXXXXX XXXXXX XXXXXXXX
			Surgical		DDMMMYYYY	DDMMMYYYY		
XXX-XXX	XXX	Screen	Medical	XXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	NO	

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.5 Nicotine Use (Safety Population)

Subject Number	Study Period	Substance	Description of Use	Start Date	End Date
XXX-XXX	Screen	XXXXXXXX XXX	XXXXX XXXXXXX XXXXXX	DDMMMYYYY	DDMMMYYYY

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.1.1 Inclusion Criteria

1. Healthy, adult, male or female (of non-childbearing potential only), 18-55 years of age, inclusive, at screening.
2. < >
3. < >
4. < >
5. < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.1.2 Exclusion Criteria

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. < >
3. < >
4. < >
5. < >
6. < >
7. < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2 Subject Eligibility (Safety Population)

Subject Number	Study Period	Did subject meet all eligibility criteria?	Specify
XXX-XXX	Screen	YES	
XXX-XXX	Screen	NO	<this column is only presented if data is present>

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3.1 Check-in Criteria

1. Did the Subject report any study restriction violations since the last study visit?
2. IF YES TO ANY QUESTION, WAS SUBJECT APPROVED FOR STUDY?

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3.2 Check-in Responses (Safety Population)

Subject Number	Treatment Sequence	Study Period	Day	Hour	Date	Time	Check-in Criteria X	Check-in Criteria X	Specify
XXX-XXX	AB	1	X	Check-in	DDMMMYYYY	hh:mm	YES	YES	<this column prints only if data is present>

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4.1 Test Compound Description

Treatment	Compound	Form	Route
A	XXXXXXXXXXXXX	< >	XXXX
B	XXXXXXXXXXXXX	< >	XXXX

<similar for Treatments C and D>

Programmer Note: Compound Name should be the actual compound (EXTRT) and dosage (EXTDOSE) administered (ie, per SDTM EX)

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4.2 Test Compound Administration Times (Safety Population)

Subject Number	Study Period	Treatment	Day	Hour	Start Date	Start Time	Compound	Dosage	Comments
XXX-XXX	1	X	X	0	DDMMMYYYY	HH:MM:SS	XXXXXXXXX	< >	<Only populate if there are
	2	X	X	0	DDMMMYYYY	HH:MM:SS	XXXXXXXXX	< >	comments present in the data>

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Programmer Note: Compound Name should be the actual compound (EXTRT) administered (ie, per SDTM EX)

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.5 PK Blood Draw Times (Safety Population)

Subject Number	Study Period	Treatment	Day	Hour	Date	Actual Time	Bioassay	Comments
XXX-XXX	1	X	1	-X.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
			2	XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
			3	XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.6 Meal Times (Safety Population)

Subject Number	Study Period	Treatment	Day	Hour	Event	Date	Start Time	Stop Time	Comments
XXX-XXX	1	A	-X	-XX.XX	LUNCH	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	DINNER	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	SNACK	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
			X	XX.XX	LUNCH	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	DINNER	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	SNACK	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
			X	XX.XX	BREAKFAST	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	LUNCH	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	DINNER	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
	2	B	-X	-XX.XX	LUNCH	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	DINNER	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	SNACK	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
			X	XX.XX	BREAKFAST	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				XX.XX	LUNCH	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				XX.XX	DINNER	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	SNACK	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
			X	XX.XX	BREAKFAST	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	LUNCH	DDMMMYYYY	XX:XX:XX	XX:XX:XX	
				-XX.XX	DINNER	DDMMMYYYY	XX:XX:XX	XX:XX:XX	

Note: Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.7 Prior and Concomitant Medications (Safety Population)

Subject Number	Treatment	Any Med^?	Prior to Study?	Medication (WHO* Term)	Dosage	Route	Frequency	Start Day/Date/Time	Stop Day/Date/Time	Indication	AE No. (If Due to AE)	Continuing Medication?
XXX-XXX		No		None								
XXX-XXX	X	Yes	Yes	ACETAMINOPHEN (ACETAMINOPHEN)	620 mg	BY MOUTH	AS NEEDED	XX/DDMMMYYYY/ HH:MM	XX/DDMMYYYY/ HH:MM	XXXXX	XXX	YES

Note: * Concomitant medications are coded with WHO Dictionary Version 01-Mar-2019 b3.
^ Med = Medication; UNK = Unknown
Prior medication was medication taken prior to study drug administration.
Start and stop day is relative to Period 1 Day 1.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.1 Adverse Events (I of II) (Safety Population)

Subject Number	Treatment	TE?^	Adverse Event/ Preferred Term*	Time from Last Dose (DD:HH:MM)	Onset Day	Onset Date	Onset Time	Resolved Day	Resolved Date	Resolved Time	Duration (DD:HH:MM)
XXX-XXX		None									
XXX-XXX	X	Yes	XXXXXXXXXXXX/ XXXXXXXXXX	XX:XX:XX	XX	DDMMMYYYY	X:XX	XX	DDMMMYYYY	X:XX	XX:XX:XX
		No	XXXXXXXXXXXX/ XXXXXXXXXX	XX:XX:XX	XX	DDMMMYYYY	X:XX	XX	DDMMMYYYY	X:XX	XX:XX:XX

Note: * Adverse events are classified according to MedDRA Version 22.0 by System Organ Class and Preferred Term.
^ TE = Treatment-emergent, Onset and resolved day is relative to Period 1 Day 1.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.2 Adverse Events (II of II) (Safety Population)

Subject Number	Treatment	Adverse Event	Onset Day	Onset Date	Onset Time	Freq^	Severity	Ser*	Outcome	Action for LOXO-292	Action for Moxifloxacin	Other Action Taken	Relationship to LOXO-292	Relationship to Moxifloxacin
XXX-XXX		None												
XXX-XXX	X	XXXXXXX	XX	DDMMMYYYY	XX:XX	Inter.	Grade 1	NO	Resolved	Dose Not Changed	Dose Not Changed	None	Not Related to LOXO-292	Not Related to Moxifloxacin

Note: Ser* = Serious; Freq^ represents Frequency: SI = Single Episode, Inter. = Intermittent, Cont. = Continuous
Severity/Intensity: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to AE
Not all grades are appropriate for all AEs, therefore some AEs are listed in the CTCAE with fewer than 5 options for grade selection.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.3 Adverse Event Non-Drug Therapy (Safety Population)

Subject Number	Treatment	Adverse Event	Onset Day	Onset Date	Onset Time	Resolved Day	Resolved Date	Resolved Time	Therapy Date	Therapy Time	Therapy Description
XXX-XXX	X	DRY LIPS	XX	DDMMMYYYY	X:XX	XX	DDMMMYYYY	X:XX	DDMMMYYYY	XX:XX	PETROLEUM JELLY

Note: Onset and resolved day is relative to Period 1 Day 1.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.4 Adverse Event Preferred Term Classification (Safety Population)

Subject Number	Treatment	Adverse Event	Preferred Term*	Body System	Onset Day	Onset Date	Onset Time
XXX-XXX	X	XXXXXXX XXXXX XXXX XXXXXX	XXXXXXXXXX XXXXXXX	XXXXXXXXXXXXXXXXXXXX	XX	DDMMMYYYY	X:XX

Note: * Adverse events are classified to MedDRA Version 22.0 by System Organ Class and Preferred Term.
Onset day is relative to Period 1 Day 1.
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendices 16.2.8.1.2-16.2.8.1.4 will have the following format.

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Appendix 16.2.8.1.1 Clinical Laboratory Report – Serum Chemistry (Safety Population)

Subject Number	Age$/ Sex	Treatment Sequence	Study Period	Day	Hour	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)
XXX-XXX	XX/M	XXXX	Screen			DDMMMYYYY	XX HN	XX	XX	XX	XX HN
			1	-X	CHECK-IN	DDMMMYYYY	XX	XX	XX	XX	XX
				X	X	DDMMMYYYY	XX	XX	XX	XX HN	XX
			2	X	X	DDMMMYYYY	XX	XX	XX	XX	XX
				X	X	DDMMMYYYY	XX LY-	XX LN	XX	XX LY-	XX

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early term chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for.
Arrange alphabetically by lab test name.
Add fourth flag in the cases that ^ or R are used for the PI flag. This flag will be found in the ClinQuick Extraction

Note: $ Age is calculated from the date of first dosing.
H = Above Reference Range, L = Below Reference Range
Computer Clinical Significance: N = Not Clinically Significant, Y = Clinically Significant
PI Interpretation: - = Not Clinically Significant, R = To be Rechecked, ^ = Will be Retested at a Later Event
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.5 Clinical Laboratory Report - Comments (Safety Population)

Subject Number	Treatment Sequence	Study Period	Day	Hour	Date	Department	Test	Result	Unit	Comment
XXX-XXX	XXXX	X	X	-X.X	DDMMMYYYY	Other Tests	Fibrinogen	XXX	mg/dL	Not significant in the context of this study.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.2 Vital Signs (Safety Population)

Subject Number	Study Period	Treat-ment	Day	Hour	Date	Time	Blood Pressure (mmHg) Position	Arm	Sys/Dia	Pulse (bpm)	Respir-ation (rpm)	Temper-ature (°C)	Weight (kg)	Comments
XXX-XXX	Screen				DDMMMYYYY	X:XX:XX							XXX.X	
					DDMMMYYYY	X:XX:XX	SUPX	Right	XXX/ XX	XX	XX	XX.X		
	X	X	-X	Check-in	DDMMMYYYY	XX:XX:XX							XXX.X	
					DDMMMYYYY	XX:XX:XX	SUPX	Right	XXX/ XX	XX	XX			
			X	X.X	DDMMMYYYY	XX:XX:XX	SUPX	Right						
				X.X	DDMMMYYYY	XX:XX:XX	SUPX	Right						
				X.X	DDMMMYYYY	X:XX:XX	SUPX	Right	XXX/ XX	XX	XX			
				X.X	DDMMMYYYY	X:XX:XX	SUPX	Right	XXX/ XX	XX	XX			
				X.X	DDMMMYYYY	X:XX:XX	SUPX	Right	XXX/ XX	XX	XX			
				R	DDMMMYYYY	XX:XX:XX	SUPX	Right	XXX/ XX	XX	XX			
				X.X	DDMMMYYYY	XX:XX:XX	SUPX	Right						

Programmer note: Sort unscheduled assessment and early term chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for.

Note: SUPX = X-minute supine, R = Recheck Value, Sys/Dia = Systolic/Diastolic, rpm = breaths per minute
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.3 12-Lead Electrocardiogram (Safety Population)

Subject Number	Study Period	Treatment	Day	Hour	Date	Time	Result	Heart Rate (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTcF* (msec)	Comments
XXX-XXX	Screen		.		DDMMMYYYY	X:XX:XX	NORMAL	XX	XXX.X	XX.X	XXX.X	XXX.X	
	1	X	-1	Check-in	DDMMMYYYY	X:XX:XX	NORMAL	XX	XXX.X	XX.X	XXX.X	XXX.X	
				X.XX	DDMMMYYYY	X:XX:XX	NORMAL	XX	XXX.X	XX.X	XXX.X	XXX.X	
	2	X	X	X.XX	DDMMMYYYY	X:XX:XX	NORMAL	XX	XXX.X	XX.X	XXX.X	XXX.X	
				X.XX	DDMMMYYYY	X:XX:XX	NORMAL	XX	XXX.X	XX.X	XXX.X	XXX.X	
			X	X.XX	DDMMMYYYY	X:XX:XX	NORMAL	XX	XXX.X	XX.X	XXX.X	XXX.X	#
			X	^ X.XX	DDMMMYYYY	X:XX:XX	NORMAL	XX	XXX.X	XX.X	XXX.X	XXX.X	@

Programmer note: Sort unscheduled assessment and early term chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for.

Note: NCS = Abnormal, Not Clinically Significant
QTcF* = QT corrected for heart rate using Fridericia's correction.
= QTcF > 450, @ = QTcF change from baseline greater than 30 msec
^ = Repeat assessment or unscheduled event
Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.4 Holter Monitoring Times (Safety Population)

Subject Number	Study Period	Start				Stop				Comment
		Day	Hour	Date	Time	Day	Hour	Date	Time	
XXX-XXX	X	X	XX.XX	DDMONYYYY	XX:XX	X	XX.XX	DDMONYYYY	XX:XX	<Only present if populated >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.5 Phone Call (Safety Population)

Subject Number	Study Period	Day	Phone Call Completed?	Date	Time	If no, reason
XXX-XXX	X	X	Yes/No	DDMMMYYYY	HH:MM	Wrong number

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Statistical Analysis Plan

A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects

Protocol: LOXO-RET-18032

Sponsor: Loxo Oncology, Inc.

ERT Internal ID: 266-1001

Version: Final 1.0
Authors: PPD, MS, Biostatistician I
PPD, PhD, Senior Biostatistician

Date: 22 July 2019

Revision History

Version	Issue Date	Author(s)	Description
Draft 0.1	23 May 2019	PPD and PPD	Initial version for review.
Draft 0.2	17 June 2019	PPD and PPD	Revised version.
Draft 0.3	10 July 2019	PPD	Revised version to add testing for carryover effect.
Draft 0.4	19 July 2019	PPD	Revised version.
Final 1.0	22 July 2019	PPD	Final version.

Table of Contents

1 Abbreviations

Abbreviation	Term/Description
bpm	Beats per minute
CI	Confidence interval
C_{max}	Maximum plasma concentration
C-QT	Concentration-QTc
Δ	Change-from-baseline
ΔΔ	Placebo-corrected change-from-baseline
ECG	Electrocardiogram
HR	Heart rate
LOESS	Locally weighted scatter plot smoothing
LS	Least squares
ms	Millisecond
PK	Pharmacokinetic(s)
PR	PR interval of the ECG
Q-Q	Quantile-quantile
QRS	QRS interval of the ECG
QT	QT interval of the ECG
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
QTcP	Population heart rate-corrected QT interval
RR	RR interval of the ECG
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
TQT	Thorough QT

2 Introduction

This statistical analysis plan (SAP) was developed after review of the protocol LOXO-RET-18032 (Final version dated 03 April 2019) for the study "A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of LOXO-292 on the QTc Interval in Healthy Adult Subjects" and the ERT contract/proposal. This document defines the populations to be analyzed and provides full details of the statistical analyses, data displays, and algorithms to be used for data derivations to aid in the production of the statistical output and the statistical section of the cardiac safety report in regard to electrocardiogram (ECG) and concentration-QTc analyses. Relevant subject characteristics as well as the electrocardiographic parameters that will be evaluated are described along with the specific statistical methods.

3 Study Design

This is a single-dose, randomized, double-blind (except for the use of moxifloxacin), placebo- and positive-controlled, 4-way crossover study. Thirty-two, healthy, adult male and female (women of non-childbearing potential only) subjects will be enrolled.

Screening of subjects will occur within 28 days prior to the first dosing. On Day 1, subjects will be randomized to 1 of 4 treatment sequences.

On Day 1 of each period, subject will receive 1 of 2 single oral dose levels of LOXO-292, a single oral dose of moxifloxacin, or a single oral dose of LOXO-292 matching placebo on 1 occasion, according to a randomization scheme. Cardiodynamic samples will be collected pre-dose and for up to 24 hours post-dose as outlined below. Pharmacokinetic (PK) samples will be collected pre-dose and for up to 24 hours post-dose for moxifloxacin and up to 240 hours post-dose for LOXO-292, as per treatment received. There will be a washout period of 10 days between dosing in each period.

Safety and tolerability will be assessed through end of treatment or early termination by monitoring adverse events, performing physical examinations and clinical laboratory tests, measuring vital signs, and recording ECGs.

4 Cardiodynamic ECG Assessment

Holter monitors will be used to collect continuous 12-lead ECG data for the purpose of collecting cardiodynamic ECGs for approximately 26 hours. Recording will be started and stopped at logistically optimal times to ensure that all scheduled time points are collected. At least three 12-lead ECG recordings will be extracted from the Holter monitor data on Day 1 of each period within a 5-minute time window around the scheduled time points, but prior to the PK blood sample collection.

The time points for ECG extraction in each period are 0.75, 0.5, and 0.25 hours prior to dosing on Day 1 and 0.25, 0.5, 0.75, 1.5, 2, 2.5, 3, 4, 7, 9, 12, and 24 hours post-dose (the 24 hours post-dose time point will occur on Day 2, at the end of the Day 1 Holter recording).

Timing and recording technique for ECGs will be standardized for all subjects. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli (e.g., TV, loud radio, interactions with other participants, etc.) for at least 10 minutes before and 5 minutes during the ECG extraction to allow for quality ECG extraction. All ECG extraction should occur in a 5-minute time window around the scheduled/nominal time. If targeted ECG time points are artefactual or of poor quality, analyzable 10-second ECGs will be extracted as close as possible to the targeted time points.

Nominal time of the ECG recording will be used for the cardiodynamic analyses.

All Holter/ECG data will be collected using M12R continuous 12-lead digital recorders and the M12A Enterprise Holter System Client (Global Instrumentation, LLC, Manlius, New York, USA). The equipment will be supplied and supported by ERT.

ECG intervals will be measured by the core laboratory in a blinded manner using the Expert Precision QT technique (see Appendix A for more details). The ECG database will be locked before any statistical analysis is undertaken.

4.1 Cardiodynamic ECG Objectives

For the purpose of this analysis plan, objectives related to ECG assessment are described.

4.1.1 Primary Objective

The primary ECG objective is to evaluate the effects of therapeutic and supratherapeutic exposure of LOXO-292 on the QTc interval by assessing concentration-QT relationship using exposure-response modelling.

4.1.2 Secondary Objectives

- To assess the effect of therapeutic and supratherapeutic exposure of LOXO-292 on other ECG parameters (heart rate [HR], PR, and QRS interval);
- To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control in healthy adult subjects;
- To assess the effect of therapeutic and supratherapeutic exposure of LOXO-292 on categorical outliers for HR, PR, and QRS interval.

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4.2 Cardiodynamic ECG Endpoints

4.2.1 Primary Endpoint

The primary endpoint is the effect of LOXO-292 plasma concentrations on the QTc interval using linear mixed-effect exposure-response modeling, including the predicted ΔΔQTc at C_{max} values corresponding to exposure levels of interest.

4.2.2 Secondary Endpoints

The secondary endpoints are:

- The change in other ECG parameters such as such as QT, PR, and RR intervals, QRS duration, and HR.
- Morphological changes of ECG waveform (e.g., T-wave morphology and presence of pathologic U wave).
- Determination of assay sensitivity using exposure-response modeling of the ΔΔQTc following moxifloxacin administration.

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5 Statistical Methods

5.1 General Methodology

All statistical analyses will be performed using the statistical software SAS for Windows Version 9.4 or higher (SAS Institute, Inc., Cary, NC). In all calculations, zero will be substituted for concentrations below the quantification limit of the assay and for concentrations from subjects who received placebo. Data collected from all randomized subjects will be presented in data listings. Both absolute values and change-from-baseline values for each subject will be given where applicable. All continuous data will be listed with the same precision as will be presented in the database. Data listings will be sorted by treatment, subject ID, and time point. Missing values will be represented by an empty cell and no imputation will be made.

Continuous data will be summarized using descriptive statistics including number of subjects (n), mean, median, standard deviation (SD), standard error (SE), 90% confidence interval (CI), minimum, and maximum by treatment and time point. Mean and median values will be rounded to the nearest tenth, or to the first non-zero decimal. SD, SE, and CI will be rounded to the nearest hundredth, or to 1 digit more than the nearest non-zero digit. For the concentration-QTc analysis, 3 significant digits will be kept for the effect estimates. *P* values will be reported with 4 digits and *P* values less than 0.0001 will be reported as < 0.0001. Categorical data will be summarized 2 ways, by subject and by time point. Subject data will be summarized using the count of distinct subjects that fall into the category and the percentage of the total number of subjects. Time point data will be summarized using the count of time points at which the assessments fall into the category and the percentage of the total number of time points at

which assessments are performed. Percentages will be rounded up or down to the nearest tenths decimal place. Counts (either number of subjects or number of time points) for each treatment will be used as the denominator in the calculation of percentages unless otherwise specified.

5.2 Analysis Populations

The analysis populations for cardiodynamic ECG assessment are defined as follows (Table 1).

Table 1 Analysis populations for cardiodynamic ECG assessment

Population	Subjects
Safety population	All subjects enrolled in the study who receive at least 1 dose of study drug (LOXO-292, moxifloxacin, or placebo).
PK population	All subjects who receive a dose of LOXO-292 or moxifloxacin and have at least 1 evaluable PK plasma concentration of LOXO-292 or moxifloxacin.
Cardiodynamic population	All subjects in the Safety population with measurements at baseline as well as on-treatment with at least 1 post-dose time point with a valid ΔQTcF value. The Cardiodynamic population will be used for the by-time point and categorical analyses of the cardiodynamic ECG parameters.
C-QT population	All subjects who are in both the PK and Cardiodynamic populations with at least 1 pair of post-dose PK and QTcF data from the same time point as well as subjects in the Cardiodynamic population who received placebo. The C-QT population will be used for the concentration-QTc analysis. This population will be defined separately for LOXO-292 and for moxifloxacin.

5.3 Baseline

For all continuous ECG parameters from each period, baseline is defined as the average of the measured ECG intervals from the 3 pre-dose time points (0.75, 0.5, and 0.25 hours before dosing) on Day 1 for the respective period.

5.4 QT Correction Methods

The QT and RR value for each beat will be used for HR correction. Replicate ECGs will be extracted in up to 10 replicates from each nominal time point prespecified in the protocol. The median value from each extracted replicate from evaluable beats will be calculated, and then the average of all available medians (minimum 3 medians) from a nominal time point will be used as the subject's reportable value at that time point.

The Fridericia's correction QTcF is defined as $QTcF = QT/RR^{1/3}$.

In case a substantial heart rate effect (i.e., largest mean ΔΔHR > 10 bpm) is observed, additional QT correction methods, including the population heart rate-corrected QT interval (QTcP as described by Tornøe et al[1]), will be considered.

6 Analyses

6.1 Carryover Effect Test

Before the concentration-QTc analysis in Section 6.2 is performed, it is necessary to test the carryover effect, even the possibility that some subjects receiving placebo may have small residual exposures to LOXO-292 present. A mixed-effect repeated measures model will be considered with ΔQTcF as the dependent variable; period, time (i.e., post-dose time points), treatment (therapeutic dose of LOXO-292, supratherapeutic dose of LOXO-292, and placebo), time-by-treatment interaction, period-by-treatment interaction, period-by-time interaction, and period-by-treatment-by-time as fixed effects, and baseline QTcF as a covariate. An unstructured covariance matrix will be specified for the repeated measures at post-dose time points for subject within treatment period. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. The model will also include a subject-specific random effect. If the period-by-treatment interaction (and period-by-treatment-by-time interaction if necessary) is not statistically significant at the significance level 5%, this indicates that there is no carryover effect. Then the proposed concentration-QTc analysis (as well as by-time point analysis and categorical analysis) will be performed, and zero will be substituted for concentrations below the quantification limit of the assay and for concentrations from subjects who received placebo. Otherwise, a sensitivity analysis(es) of concentration-QTc, by-time point, and categorical analyses will be performed by excluding period(s) with observed non-zero concentrations at baseline for subjects receiving placebo. Additional sensitivity analyses may exclude subjects with more than extremely low LOXO-292 concentrations.

6.2 Concentration-QTc Analysis (Analysis of Primary Endpoint)

The concentration-QTc analysis will be based on the C-QT population. The relationship between LOXO-292 plasma concentration and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects model with ΔQTcF as the dependent variable, LOXO-292 plasma concentration as the explanatory variate (0 for placebo), centered baseline QTcF (i.e., baseline QTcF for individual subject subtracting the population mean baseline QTcF for all subjects in the same period) as an additional covariate, study treatment (active = 1 or placebo = 0), and time (i.e., post-dose time point) as categorical factors, and a random intercept and slope per subject (Garnett et al[2]). The degrees of freedom for the model estimates will be determined by the Kenward-Roger method. From the model, the slope (i.e., the regression parameter for the concentration) and the treatment effect-specific intercept (defined as the difference between active and placebo) will be estimated together with the 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

The geometric mean of the individual C_{max} values for LOXO-292 plasma concentrations for subjects in each of the LOXO-292 dose groups will be determined, respectively. The predicted effect and its 2-sided 90% CI for ΔΔQTcF (i.e., slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained. If the upper bound of the 2-sided 90% CI of the model-predicted QTc effect is below 20 ms at clinically relevant plasma levels of LOXO-292, it will be concluded that LOXO-292 does not cause clinically concerning QTc prolongation within the observed plasma concentration ranges.

The plot of the observed median-quantile LOXO-292 concentrations and associated mean placebo-adjusted ΔQTcF (i.e., ΔΔQTcF) with 90% CI adjusted for diurnal effects, together with the regression line presenting the predicted ΔΔQTcF (90% CI) (as described by Tornøe et al[1]) will be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration-QTc relationship. The observed ΔQTcF values from the active groups will be adjusted by the estimated time effect from the concentration-QTc model (i.e. the estimated diurnal effect under the placebo treatment). The individually estimated placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with LOXO-292 at time point j minus the estimation of time at time point j (i.e., time effect). Additional plots will be used to validate the model assumptions. For evaluation of the heart rate-corrected QT interval, a scatter plot and quantile plot of QTcF and RR intervals by treatment with a regression line and a linear mixed-effects line (90% CI), respectively, will also be given. Exploratory analyses (via graphical displays and/or model fitting) will also include accounting for a delayed effect (hysteresis) and the justification for the choice of pharmacodynamics model (linear versus nonlinear).

The SAS code for the concentration-QTc analysis is as follows:

```
PROC MIXED DATA=PKPD method=reml;
CLASS SUBJID TIME;
MODEL DQTC=TRT CONC TIME CBASE/ solution cl noint alpha=0.1 alphap=0.1 COVB DDFM=KR;
RANDOM INT CONC /type=UN SUBJECT=SUBJID s;
ESTIMATE 'Pred Mean Diff for T1' TRT 1 CONC &GeoMeanCmax_1 / CL ALPHA=0.1;
ESTIMATE 'Pred Mean Diff for T2' TRT 1 CONC &GeoMeanCmax_2 / CL ALPHA=0.1;
RUN;
```

Where PKPD=C-QT population, SUBJID=subject number, TRT=treatment (active=1 or placebo=0), TIME=nominal time point, CONC=plasma concentration of LOXO-292, CBASE=centered baseline QTcF, T1= therapeutic dose of LOXO-292, T2 = supratherapeutic dose of LOXO-292, GeoMeanCmax_1=geometric mean C_{max} for therapeutic dose of LOXO-292, GeoMeanCmax_2=geometric mean C_{max} for supratherapeutic dose of LOXO-292, and DQTC=ΔQTcF.

6.2.1 Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean difference between ΔQTcF under LOXO-292 and under placebo (ΔΔQTcF) for each post-dose time point from the by-time point analysis and the mean concentration of LOXO-292 at the same time points. In addition, hysteresis plots will be given for LS mean ΔΔQTcF from the by-time point analysis and the mean concentrations. If a QT effect > 20 ms (i.e., LS mean ΔΔQTcF > 10 ms) cannot be excluded and the mean peak ΔQTcF effect is observed at the same time point and the delay between peak plasma levels and peak QT effect of more than 1 hour is present, other concentration-QTc models such as a model with an effect compartment may be explored. With the provision stated above, hysteresis will be assumed if the curve of hysteresis plot shows a counterclockwise loop. A significant treatment effect-specific intercept is not biologically plausible and therefore may be indicative of hysteresis, if it cannot be explained by a nonlinear relationship.

6.2.2 Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal Q-Q plots for the standardized residuals and the random effects, and plots of standardized residuals versus concentration, fitted values, centered baseline QTcF, nominal time, and active treatment will be produced. Scatter plots for standard residuals versus continuous covariates and box plots for standard residuals versus discrete covariates will be provided. The scatter plots of standardized residuals versus concentration, and centered baseline QTcF by LOESS fitting (i.e., locally weighted scatter plot smoothing (as described by Cleveland[3]) will also be produced with optimal smoothing parameters selected by the Akaike information criterion with a correction.[4] A scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models will be fitted, in particular an E_{max} model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

6.3 Assay Sensitivity

The analysis to show assay sensitivity will be based on the concentration-QTc analysis of the effect on ΔQTcF of CCI mg oral moxifloxacin using a similar model as for the primary analysis. That is, the relationship between moxifloxacin plasma concentration and ΔQTcF will be investigated by linear mixed-effects modeling. The model will include ΔQTcF as the dependent variable, moxifloxacin plasma concentration as the explanatory variate (0 for placebo), centered baseline QTcF as an additional covariate, study treatment (moxifloxacin = 1 or placebo = 0), and time (i.e., post-dose time point) as categorical factors, and a random intercept and slope per subject (Garnett et al[1]). The geometric mean of the individual C_{max} values for subjects receiving the single dose of CCI mg moxifloxacin will be determined. The predicted effect and its 2-sided 90% CI for ΔΔQTcF (i.e., slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

If the slope of the moxifloxacin plasma concentration/ΔQTcF relationship is statistically significant at the 10% level in a 2-sided test and the lower bound of the 2-sided 90% CI of the predicted QT effect at the observed geometric C_{max} of the CCI mg dose is above 5 ms, assay sensitivity will be deemed to have been demonstrated.

6.4 Categorical Analysis

Results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts and percentages for both number of subjects and number of time points.

A subject or time point will be determined as an outlier if the following criteria (which are assessed separately) are met for the ECG intervals (Table 2). Each subject meeting a categorical threshold will be counted once, using the largest value.

Table 2 Criteria for determining a subject or time point outlier

ECG interval	Categorical outlier criteria
QTcF	Treatment-emergent value of > 450 and ≤ 480 ms when not present at baseline (new onset)
	Treatment-emergent value of > 480 and ≤ 500 ms when not present at baseline (new onset)
	Treatment-emergent value of > 500 ms when not present at baseline (new onset)
	Increase of QTcF from baseline of > 30 and ≤ 60 ms
	Increase of QTcF from baseline > 60 ms
PR	Increase of PR from baseline > 25% resulting in PR > 200 ms
QRS	Increase of QRS from baseline > 25% resulting in QRS > 120 ms
HR	Decrease of HR from baseline >25% resulting in HR < 50 bpm
	Increase of HR from baseline >25% resulting in HR > 100 bpm

All outliers will be summarized for each treatment on the basis of incidence rates. A subject will be counted only once for a particular outlier event if the subject experiences more than 1 episode of that event. The total number of time points will be based on the number of observed time points across all subjects within a treatment group.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in all replicates at the time point. For baseline, the category will be deemed as present if observed in any replicates from all time points that constitute baseline, i.e., the 3 time points prior to dosing on Day 1 in each period.

The T-wave morphology and U-wave presence categories are described as follows (Table 3).

Table 3 T-wave morphology and U-wave presence categories (assessed manually)

Category	Description
Normal T-wave (+)	Any positive T-wave not meeting any criterion below.
Flat T-wave	T-amplitude < 1 mm (either positive or negative), including flat isoelectric line.
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave.
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive/negative and negative/positive and polyphasic T-waves included).

Category	Description
Normal T-wave (-)	T-amplitude is negative, without biphasic T-wave or notches.
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave.
U-waves	Presence of abnormal U-waves.

6.5 By-Time Point Analysis

The "by time point analysis" will be based on cardiodynamic population. The "by time point analysis" for QTcF will be based on a mixed-effect repeated measures model with ΔQTcF as the dependent variable; period, time (i.e., post-dose time point: categorical), treatment (therapeutic dose of LOXO-292, supratherapeutic dose of LOXO-292, moxifloxacin, and placebo), and time-by-treatment interaction as fixed effects; and baseline QTcF as a covariate. An unstructured covariance matrix will be specified for the repeated measures at post-dose time points for subject within treatment period. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. The model will also include a subject-specific random effect. If the fixed effect for period should prove to be not significant (i.e., if the *P* value > 0.1), the fixed effect may be removed from the model and the analysis will be repeated without period. From this analysis, the LS mean and 2-sided 90% CI will be calculated for the contrast "LOXO-292 versus placebo" at each dose of LOXO-292 and each post-dose time point, separately. If a carry-over effect is observed (Section 6.1), the period-by-treatment interaction and the period-by-treatment-by-time interaction will also be included in the model.

For HR, PR, and QRS intervals, the analysis will be based on the post-dose ΔHR, ΔPR, and ΔQRS. The same (by-time point analysis) model will be used as described for QTcF. The LS mean, SE, and 2-sided 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

The SAS code for the by-time point analysis for QTcF is as follows:

```
PROC MIXED DATA=ECG;
CLASS SUBJID TREAT TIME PERIOD SEQUENCE;
MODEL DQTC=BASE TREAT TIME TREAT*TIME PERIOD SEQUENCE/DDFM=KR;
random intercept / SUBJECT =SUBJID type=UN;
REPEATED TIME / SUBJECT = SUBJID*PERIOD type = un;
LSMEANS TREAT*TIME/CL DIFF ALPHA=0.1;
RUN;
```

Where ECG=Cardiodynamic population, SUBJID=subject identifier, TREAT=treatment (therapeutic dose of LOXO-292, supratherapeutic dose of LOXO-292, moxifloxacin, and placebo), TIME=nominal time point, BASE= baseline QTcF, PERIOD=period, SEQUENCE=sequence, and DQTC=ΔQTcF.

6.6 Determination of Sample Size

The sample size determination is based on testing to support a non-inferiority hypothesis, with a non-inferiority margin of 10 ms for this determination. Using non-inferiority margin of 10 ms, assuming a 1-sided 0.05 significance level and a common within-subject SD of 8 ms for QTc, a sample size of 30 evaluable subjects (allowing for 2 dropouts) would be expected to provide at least [redacted]% power to detect an expected mean difference of 3 ms in ΔQTc between LOXO-292 and placebo.

The proposed 4-way crossover design in this study, using 32 subjects randomized to 1 of 4 treatment sequences will result in up to 32 sets of observations each for moxifloxacin and placebo. Given what was reported in the literature, this sample size is deemed appropriate to detect a drug-induced QTc prolongation by moxifloxacin of greater than 5 ms.

7 References

1. Tornøe CW, Garnett CE, Wang Y, Florian J, Li M, Gobburu JV. Creation of a knowledge management system for QT analyses. *J Clin Pharmacol*. 2011;51(7):1035-1042.
2. Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. [Published correction appears in *J Pharmacokinet Pharmacodyn*. 2018;45(3):399]. *J Pharmacokinet Pharmacodyn*. 2018;45(3):383-397.
3. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc*. 1979;74(368):829-836.
4. Hurvich CM, Simonoff JS, and Tsai CL. Smoothing parameter selection in nonparametric regression using an improved Akaike Information Criterion. *J R Stat Soc Series B Stat Methodol*. 1998;60(2):271-293.

8 Tables, Figures, and Listings

8.1 Tables

Number	Title	Comments
14.2.3.1.1	Baseline values of ECG parameters with descriptive statistics	Number of subjects (n), mean, SD, SE, 90% CI, median, minimum, and maximum from descriptive analysis will be given by treatment for each ECG parameter.
14.2.3.1.2	Absolute values of ECG parameters with descriptive statistics	n, mean, SD, SE, 90% CI, median, minimum, and maximum from descriptive statistics will be given by treatment and post-dose time point for each ECG parameter.
14.2.3.1.3.1-14.2.3.1.3.2	Change-from-baseline QTcF, HR, PR, and QRS (ΔQTcF, ΔHR, ΔPR, and ΔQRS) at each time point	n, LS mean, SE, and 90% CI from the statistical modeling will be given by treatment and time point (Section 6.5).
14.2.3.1.4.1-14.2.3.1.4.4	Placebo-corrected change-from-baseline QTcF, HR, PR, and QRS (ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) at each time point	LS mean, SE, and 90% CI from the statistical modeling will be given by treatment and time point (Section 6.5).
14.2.3.1.5	QTcF outliers per absolute category across treatment groups	Number (%) of subjects and time points with QTcF > 450 and ≤ 480 ms, > 480 and ≤ 500 ms, and > 500 ms by treatment (Section 6.4).
14.2.3.1.6	QTcF outliers per change-from-baseline category across treatment groups	Number (%) of subjects and time points with ΔQTcF > 30 and ≤ 60 ms, and > 60 ms by treatment (Section 6.4).

Number	Title	Comments
14.2.3.1.7	Categorical analysis for HR, PR, and QRS groups	Number (%) of subjects and time points with ΔPR > 25% and PR > 200 ms at post-baseline; ΔQRS > 25% and QRS >120 ms at post-baseline; HR decrease from baseline > 25% and HR < 50 bpm at post-baseline; and HR increase from baseline > 25% and HR > 100 bpm at post-baseline (Section 6.4).
14.2.3.1.8	T-wave morphology and U-wave presence across treatment: treatment-emergent changes across treatment groups	Number (%) of subjects and time points falling into each of T-wave categories: Normal (+), Flat, Notched (+), Biphasic, Normal (-), Notched (-) as defined in Section 6.4.
14.2.3.1.9.1	Concentration-QTc analysis of LOXO-292 and associated ΔQTcF prolongation	Fixed-effect estimations and corresponding *P* values will be given (Section 6.2).
14.2.3.1.9.2	Assay sensitivity analysis of moxifloxacin and associated ΔQTcF prolongation	Fixed-effect estimations and corresponding *P* values will be given (Section 6.3).
14.2.3.1.10.1	Predicted ΔΔQTcF interval at geometric mean peak LOXO-292 concentration	Section 6.2.
14.2.3.1.10.2	Predicted ΔΔQTcF interval at geometric mean peak moxifloxacin concentration	Section 6.3.

8.2 Figures

Number	Title	Comments
14.2.3.2.1	Absolute QTcF across time points	Mean and 90% CI from descriptive analysis will be given by treatment.
14.2.3.2.2.1-14.2.3.2.2.4	Change-from-baseline QTcF, HR, PR, and QRS (ΔQTcF, ΔHR, ΔPR, and ΔQRS) across time points	LS mean and 90% CI from the statistical modeling will be shown by treatment for each parameter (Section 6.5).
14.2.3.2.3.1-14.2.3.2.3.4	Placebo-corrected change-from-baseline QTcF, HR, PR, and QRS (ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) across time points	LS mean and 90% CI from the statistical modeling will be shown by treatment (Section 6.5).
14.2.3.2.4.1	Scatter plot of QTcF versus RR by treatment	Scatter plots of QTcF and RR intervals by treatment with regression lines will be given (Section 6.2).
14.2.3.2.4.2	QTcF-RR quantile plot by treatment	QTcF-RR quantile plots (with quantiles) with linear mixed-effects line and 90% CI will be given (Section 6.2).
14.2.3.2.5.1	Plot of mean LOXO-292 plasma concentrations over time	Section 6.2.

Number	Title	Comments
14.2.3.2.5.2	Plot of mean moxifloxacin plasma concentrations over time	Section 6.3.
14.2.3.2.6	Joint plot of LOXO-292 plasma concentrations and ΔΔQTcF over time	Section 6.2.1.
14.2.3.2.7	Hysteresis plot of LOXO-292 plasma concentration and ΔΔQTcF connected in temporal order	This is what is often called a "Hysteresis plot" (Section 6.2.1).
14.2.3.2.8.1	Scatter plot of observed LOXO-292 plasma concentrations and ΔQTcF by subject	Scatter plot of ΔQTcF versus concentration with LOESS line and 90% CI and simple linear regression line (Section 6.2).
14.2.3.2.8.2	Scatter plot of observed LOXO-292 plasma concentrations and estimated placebo-adjusted ΔQTcF by subject	Scatter plot of estimated placebo-adjusted ΔQTcF versus observed concentration and linear mixed-effect regression line with CI (Section 6.2).
14.2.3.2.8.3	Scatter plot of observed moxifloxacin plasma concentrations and ΔQTcF by subject	Scatter plot of ΔQTcF versus concentration with LOESS line and 90% CI and simple linear regression line (Section 6.3).
14.2.3.2.8.4	Scatter plot of observed moxifloxacin plasma concentrations and estimated placebo-adjusted ΔQTcF by subject	Scatter plot of estimated placebo-adjusted ΔQTcF versus concentration and linear mixed-effect regression line with CI (Section 6.3).
14.2.3.2.9.1	Model-predicted ΔΔQTcF (mean and 90% CI) and estimated placebo-adjusted ΔQTcF (mean and 90% CI) across deciles of LOXO-292 plasma concentrations	Section 6.2.
14.2.3.2.9.2	Model-predicted ΔΔQTcF (mean and 90% CI) and estimated placebo-adjusted ΔQTcF (mean and 90% CI) across deciles of moxifloxacin plasma concentrations	Section 6.3.
14.2.3.2.10.1	Predicted ΔΔQTcF interval at geometric mean peak LOXO-292 concentrations	Section 6.2.
14.2.3.2.10.2	Predicted ΔΔQTcF interval at geometric mean peak moxifloxacin concentrations	Section 6.3.
14.2.3.2.11.1	Scatter plot of standardized residuals versus fitted values for LOXO-292	Section 6.2.2.
14.2.3.2.11.2	Scatter plot of standardized residuals versus fitted values for moxifloxacin	Section 6.3.

Number	Title	Comments
14.2.3.2.12.1	Scatter plot of standardized residuals versus LOXO-292 concentrations with LOESS	Section 6.2.2.
14.2.3.2.12.2	Scatter plot of standardized residuals versus moxifloxacin concentrations with LOESS	Section 6.3.
14.2.3.2.13.1	Scatter plot of standardized residuals versus centered baseline QTcF with LOESS for LOXO-292	Section 6.2.2.
14.2.3.2.13.2	Scatter plot of standardized residuals versus centered baseline QTcF with LOESS for moxifloxacin	Section 6.3.
14.2.3.2.14.1	Box plot of standardized residuals versus nominal time for LOXO-292	Section 6.2.2.
14.2.3.2.14.2	Box plot of standardized residuals versus nominal time for moxifloxacin	Section 6.3.
14.2.3.2.15.1	Box plot of standardized residuals versus treatment for LOXO-292	Section 6.2.2.
14.2.3.2.15.2	Box plot of standardized residuals versus treatment for moxifloxacin	Section 6.3.
14.2.3.2.16.1	Normal Q-Q plot of standardized residuals for LOXO-292	Section 6.2.2.
14.2.3.2.16.2	Normal Q-Q plot of standardized residuals for moxifloxacin	Section 6.3.
14.2.3.2.17.1	Normal Q-Q plots of the estimated random effects for LOXO-292	Section 6.2.2.
14.2.3.2.17.2	Normal Q-Q plots of the estimated random effects for moxifloxacin	Section 6.3.

8.3 Listings

Number	Title	Comments
16.2.6.3.1 - 16.2.6.3.4	QTcF, HR, PR, and QRS parameters – absolute and change-from-baseline values	Section 6.5.
16.2.6.4	T-wave morphology and U-wave presence	Section 6.4.
16.2.6.5	ΔQTcF and time-matched concentrations of LOXO-292 and moxifloxacin for each subject	Data for concentration-QTc (Section 6.2) and assay sensitivity (Section 6.3).

9 Approvals

ERT

PPD

PPD MD, PhD
Chief Scientific Officer, Cardiac Safety

22 JUL 2019
Date

PPD

PPD PhD
Senior Biostatistician

22 Jul 2019
Date

PPD

Project Manager

22 JUL 2019
Date

Loxo Oncology, Inc.

PPD

Director, Biostatistics

24-Jul-19 | 18:15:46 PDT
Date

Signing Time: 7/24/2019 9:15:43 PM EDT
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Appendix A: Expert Precision QT Analysis

Expert Precision QT analysis (formerly High Precision QT analysis) will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates (1 replicate consists of one 14 second ECG). Statistical quality control procedures will be used to review and assess all beats and identify "high" and "low" confidence beats using several criteria including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely)
- RR values exceeding or below certain thresholds (biologically unlikely)
- Rapid changes in QT, QTc, or RR from beat to beat

Placement of fiducials and measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates will be performed using the iCOMPAS software. All beats that are deemed "high confidence" will not be reviewed by an ERT ECG analyst. All low confidence beats will be reviewed manually by an ERT ECG analyst and adjudicated using pass-fail criteria. The beats found acceptable by manual review will be included in the analysis. The beats confirmed to meet fail criteria will not be included in the analysis.

For the purpose of measuring PR and QRS intervals and to assess T-wave morphology and presence of U-waves, the TQT Plus algorithm will select the 3 ECG replicates with the highest quality score from the ECG extraction window. These 3 ECGs will be analyzed using a semi-automated process to determine these parameters. If 3 consecutive usable beats cannot be identified in at least 2 of the 3 replicates, then all beats in all replicates will be reviewed for that time point using a manual analysis.

If manual analysis is required, then all beats in a minimum of 3 replicates will be reviewed using the iCOMPAS software. The ERT ECG analyst will review all usable beats in Lead II (or an alternate lead) for each replicate and will review and/or adjust the fiducial placements (onset of P, onset of Q, offset of S, and offset of T-wave that were electronically marked) of each waveform and also document the T-wave morphology and the presence of U-waves for each beat. A replicate will only be reported if it has 3 approved, usable beats.