Statistical Analysis Plan J2G-OX-JZJR (2)

An Open-Label, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of LOXO-292 on the Single Dose Pharmacokinetics of Midazolam in Healthy Adult Subjects

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Statistical Analysis Plan

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Compound Name: LOXO-292

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Statistical Analysis Plan Signature Page

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1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from study LOXO-RET-18017. 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 exploratory 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

Primary:

To investigate the effect of multiple-dose LOXO-292 on the single-dose pharmacokinetics (PK) of midazolam, a sensitive cytochrome P450 (CYP) 3A (CYP3A4) substrate, in healthy adult subjects.

Secondary:

1. To evaluate the single-dose PK of LOXO-292 administered alone and the multiple-dose PK of LOXO-292 with and without coadministration of midazolam in healthy adult subjects.

2. To determine the safety and tolerability of multiple-dose LOXO-292 alone and when coadministered with a single-dose of midazolam in healthy adult subjects.

2.2 Endpoints

Pharmacokinetics:

The following PK parameters will be calculated for midazolam and 1-hydroxymidazolam (1-OH-midazolam) in plasma in Period 1, CCI and Period 2, CCI : AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F (midazolam only), and Vz/F (midazolam only).

The following PK parameters will be calculated for LOXO-292 in plasma in Period 2, on CCI (following morning dosing): AUC0-12, Cmax, and Tmax; and on CCI , and CCI (following morning dosing): AUCtau, AUC0-24 (on CCI only),

Cmax,ss, Tmax,ss, and CL,ss/F. Additionally, Ctrough values will be assessed following the 2nd dose on CCI [redacted].

An analysis of variance (ANOVA) will be performed on the midazolam and 1-OH-midazolam natural log (ln) transformed AUC0-t, AUC0-inf, and Cmax, using the appropriate statistical procedure.

Safety:

Safety will be monitored through 12 lead electrocardiograms (ECGs), physical examination, vital sign measurements, pulse oximetry, clinical laboratory tests, and adverse events (AEs). Incidence of AEs and number of subjects with AE will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

3. STUDY DESIGN

This was an open label, 2-period, fixed-sequence study.

Sixteen (16), healthy, adult male and female (women of non-childbearing potential only) subjects were enrolled. Every attempt was made to enroll at least 3 subjects of each sex.

Screening of subjects occurred within 28 days prior to the first dosing (i.e., midazolam).

In Period 1, Day 1, a single oral dose of midazolam was administered. PK samples for midazolam and 1-OH-midazolam were collected predose and for 24 hours postdose.

In Period 2, oral doses of LOXO-292 were administered twice daily (BID) for 10 consecutive days (Days 1 to 10) with a single oral dose of midazolam coadministered on Day 10. PK samples for midazolam and 1-OH-midazolam were collected predose and for 24 hours following midazolam dosing on Day 10. PK samples for LOXO-292 were collected CCI [redacted].

There was a washout period of 48 hours between midazolam dose in Period 1 and the first LOXO-292 dose in Period 2.

Safety was monitored throughout the study by repeated clinical and laboratory evaluations.

Subjects were permitted to be replaced at the discretion of the Sponsor, however no subjects were replaced in this study.

Subjects were housed throughout the study beginning in Period 1, Day -1, at the time indicated by the clinical research unit (CRU), until after completion of the 24-hour blood draw and/or study procedures in Period 2, Day 11.

The CRU made every attempt to contact all subjects who received at least one dose of study drug (including subjects who terminated the study early) using their standard procedures (i.e., phone call or other method of contact) approximately 7 days after the last study drug administration (midazolam or LOXO-292, whichever came last) to determine if any AE had occurred since the last study 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 midazolam and LOXO-292 will 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 criteria, deviate significantly from the protocol, or have unavailable or incomplete data which 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 was supplied as 80 mg capsules.

Midazolam was supplied as midazolam HCl 2 mg/mL syrup, equivalent to 2 mg/mL of midazolam.

Each dose of LOXO-292 and midazolam were administered orally with 240 mL of room temperature water. When LOXO-292 and midazolam were administered concurrently, only 240 mL of room temperature water was administered for both drugs. The dose of midazolam in Period 1, Day 1 and the coadministered morning doses of LOXO-292 and midazolam in Period 2, Day 10 were preceded by an overnight fast of at least 10 hours. All other doses were preceded by a 2-hour fast.

Subjects were instructed not to crush, split, or chew LOXO-292.

All Subjects (n = 16)

Table 5.1 Treatment Description

Treatment	Short Description (text, tables headers, figures, listings, SAS output)	Description
A (Period 1)	2 mg midazolam	A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
B* (Period 2)	2 mg midazolam + MD 160 mg LOXO-292	Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of CCI
B1	MD 160 mg LOXO-292 Alone	Multiple doses of 160 mg LOXO-292 BID from Day 1 to CCI
B2	2 mg midazolam + MD 160 mg LOXO-292	Multiple doses of 160 mg LOXO-292 BID on CCI with a single dose of 2 mg midazolam coadministered on the morning of CCI

* For AEs, Treatment B will be divided into two segments as B1 and B2.
MD = multiple dose

6. PHARMACOKINETIC ANALYSIS

6.1 Measurements and Collection Schedule

Blood samples for PK assessment of midazolam and 1-OH-midazolam were taken at the following time points on Day [redacted]

Blood samples for PK assessment of LOXO-292 were taken at the following time points after the morning dose on Days [redacted]. Trough samples were taken following the [redacted]

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 Midazolam

Plasma concentrations of midazolam and 1-OH-midazolam 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 midazolam and 1-OH-midazolam is 0.100 – 100 ng/mL.

6.2.2 LOXO-292

Plasma concentrations of LOXO-292 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 (LLOQ – ULOQ) for LOXO-292 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.

6.3 Investigational Product and PK Analyte Information

6.3.1 Midazolam

Midazolam was supplied as midazolam HCl syrup 2 mg/mL, each mL contained 2 mg of midazolam (freebase).

6.3.2 LOXO-292

LOXO-292 has a molecular weight of approximately 500 g/mol. LOXO-292 was supplied as a powder-in-capsule containing 80 mg of drug substance (freebase) and as a simple blend with excipients in a hard gelatin capsule.

6.4 Pharmacokinetic Concentrations

Plasma concentrations of midazolam, 1-OH-midazolam, and LOXO-292 as determined at the collection times and per the bioanalytical methods described in Section 6.1, Section 6.1 and Section 6.2, respectively, will be used for the calculation of the plasma midazolam, 1-OH midazolam, and LOXO-292 PK parameters.

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

The appropriate noncompartmental PK parameters will be calculated from the plasma midazolam, 1-OH-midazolam, and LOXO-292 concentration-time data using Phoenix® WinNonlin® Version 7.0 or higher. Actual sample times will be used in the calculations of the PK parameters. The calculation of the actual time for midazolam and 1-OH-midazolam will be in respect to the dose administration time of midazolam on Day 1 of Period 1 and Day 10 of Period 2. The calculation of the actual time for LOXO-292 will be in respect to the administration time of the morning LOXO-292 dose on Days 1, 9 and 10 in Period 2. All PK parameters included in the protocol are listed in Table 6.1 and 6.2 below, and are defined as appropriate for study design.

Table 6.1. Noncompartmental Pharmacokinetic Parameters to be Calculated for Midazolam and 1-OH-Midazolam

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

Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
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
t½	Apparent first-order terminal elimination half-life	Calculated as 0.693/Kel
CL/F	Apparent total plasma clearance after oral (extravascular) administration; calculated for midazolam only	Calculated as Dose/(AUC0-inf)
Vz/F	The apparent volume of distribution during the terminal elimination phase after extravascular administration; calculated for midazolam only	Calculated as Dose/(AUC0-inf x Kel)

Table 6.2. Single-dose Noncompartmental Pharmacokinetic Parameters to be Calculated for LOXO-292 on Day 1

Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
AUC0-12	Area under the concentration-time curve from time 0 to 12 hours	Calculated using the Linear Trapezoidal with Linear Interpolation Method

Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
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.

Table 6.3. Multiple-dose Noncompartmental Pharmacokinetic Parameters to be Calculated for LOXO-292 on Days 9 and 10

Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
AUCtau	Area under the concentration-time curve during a dosing interval, tau, at steady state Will be calculated after the morning dose, where tau is defined as 12 hours	Calculated using the Linear Trapezoidal with Linear Interpolation Method
Cmax,ss	The maximum observed concentration at steady state, following the morning dose	Taken directly from bioanalytical data
Ctrough*	Concentration observed at the end of a dosing interval Dosing interval is defined as 12 hours following the CC [redacted] on CCI [redacted] (corresponding to pre-morning dose samples collected on CCI [redacted])	Taken directly from bioanalytical data at any given time point
Tmax,ss	The time to reach Cmax at steady state, following the morning dose	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.
CL,ss/F	Apparent total body clearance estimated at steady state after oral/extravascular administration	Calculated as Dose/AUCtau,ss

Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
Vz,ss/F	Apparent total volume of distribution at steady state after extravascular administration	Calculated as: Dose/(AUCtau,ss x Kel)

CCI [redacted]

Pharmacokinetic 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 the statistical analysis.

For the calculation of the PK parameters, plasma concentrations below the limit of quantitation (BLQ) prior to the first quantifiable concentration will be set to 0 and plasma concentrations BLQ after the first quantifiable concentration 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, AUC%extrap, CL/F, CL,ss/F, Vz/F, and Vz,ss/F, as appropriate, 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, AUC%extrap, CL/F, CL,ss/F, Vz/F, and Vz,ss/F) may not be presented as judged appropriate and in accordance with Celerion SOPs.

6.6 Data Summarization and Presentation

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

The plasma concentrations of midazolam and 1-OH-midazolam will be listed and summarized by treatment and time point for all subjects in the PK Population. The plasma concentrations of LOXO-292 will be listed and summarized by Study Day and time point for all subjects in the PK Population. Plasma concentrations of midazolam, 1-OH-midazolam, and LOXO-292 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 midazolam and 1-OH-midazolam PK parameters will be listed and summarized by treatment for all subjects in the PK Population. Plasma LOXO-292 PK parameters will be listed and summarized by Study Day 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 midazolam, 1-OH-midazolam, and LOXO-292 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.

6.7 Statistical Analysis of PK Parameters

6.7.1 Analysis of Variance

A comparison of ln-transformed PK parameters (AUC0-t, AUC0-inf, and Cmax) of midazolam and 1-OH-midazolam will be made to evaluate the effect of multiple-dose administrations of LOXO-292 on midazolam (Treatment B Versus Treatment A) by performing an analysis of variance (ANOVA) model using PROC MIXED in SAS®. The ANOVA model will include treatment as fixed effect and subject as a random effect. The least-square means (LSMs), differences between the LSMs, and the standard error (SE) and 90% CIs associated with these differences will be determined for each parameter. These inferential results (LSMs, difference between LSMs, and

90% CIs of the difference) will be exponentiated to the original scale. Geometric LSM, geometric mean ratios (GMR), and 90% CIs will be presented.

The ANOVA analysis will be performed using the following SAS® code:

CCI

[redacted]

6.7.2 Steady-State Analysis

A steady-state analysis will be performed on the ln-transformed Ctrough concentrations for LOXO-292, on CCI [redacted], using Helmert contrasts. Additional predose Ctrough may be used for the steady-state analysis to gather more information on steady-state attainment.

Helmert contrasts are constructed such that each time point is compared to the mean of the subsequent time point. Steady state will be concluded at the time point where no more statistical difference (alpha=5%) can be observed. The contrasts will be:

CCI

[redacted]

The steady-state analysis will be conducted using PROC MIXED of SAS®. The following SAS® code will be used.

CCI

[redacted]

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 at Period 1, including rechecks and unscheduled assessments, whichever is later, unless otherwise specified in the sections below. Rechecks, unscheduled assessments and ET measurements taken after first 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 treatment 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 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 21.0.

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 and/or Midazolam.

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 and summary tables. 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. Treatment B will be divided into two segments as B1 (Multiple doses of 160 mg LOXO-292 BID from Day 1 to Day 9) and B2 (Multiple doses of 160 mg LOXO-292 BID on Day10 with a single dose of 2 mg midazolam coadministered on the morning of Day 10) (see Table 5.1). In addition, the number of AEs will be summarized. 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 the 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 Clinical Study Report.

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	Screening*
1	Day -1*
2	Day 1**
2	Day 3**
2	Day 6**
2	Day 9**
2	Day 11***

* performed following a fast of at least 12 hours
** performed prior dosing
*** performed at the end of Period 2 or prior to ET

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, a derived flag based on a search of the PI comments for a comment of "CS" or "Clinically Significant" will be used. The derived flag will be populated with "+" if the positive clinically significant determination is found in the comments for cases when the PI flag is populated with a "^" or an "R". 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. The resulting flag, e.g., G1, will be placed along with the Celerion flags (see shell of Table 14.3.4.4).

Out-of-range values and corresponding recheck results will be listed. Other lab results within this panel and time point will also be listed for this subject. Results that are indicated as CS by the PI (either in the PI flag or in PI comments) 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 in Treatment B (defined below) 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 Baseline is Day 1 predose of Treatment B (Period 2) and is the last non-missing predose measurement prior to dosing of LOXO-292, including rechecks and unscheduled assessments.

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	Parameter
Screen	Screening		HR, BP, RR, T
1	Day -1	Check-in*	HR, BP, RR, T
1	Day 1	0.75	HR, BP, RR
1	Day 1	2	HR, BP, RR
1	Day 1	4	HR, BP, RR
2	Day 1	0**	HR, BP
2	Day 1	1.5	HR, BP
2	Day 3	0**	HR, BP
2	Day 4	0**	HR, BP
2	Day 5	0**	HR, BP
2	Day 6	0**	HR, BP
2	Day 7	0**	HR, BP
2	Day 8	0**	HR, BP
2	Day 9	0**	HR, BP, RR
2	Day 9	0.75	HR, BP, RR
2	Day 9	2	HR, BP, RR
2	Day 9	4	HR, BP, RR
2	Day 10	0**	HR, BP, RR
2	Day 10	0.5	HR, BP, RR
2	Day 10	2	HR, BP, RR
2	Day 10	4	HR, BP, RR
2	Day 11	24***	HR, BP, RR, T

* performed within 24 hours prior dosing
** performed prior dosing
*** performed at the end of Period 2 or prior to ET

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 of Treatment A (Period 1) and Day 1 predose of Treatment B

(Period 2) and is the last non-missing predose measurement prior to dosing of midazolam (Treatment A) or LOXO-292 (Treatment B), including rechecks and unscheduled assessments. Note: In Period 2, respiration rate (RR) was not collected prior to Day 9. For RR, Day 9 predose will be used as baseline for Period 2. Postdose recheck values and ET results will not be used for calculation of descriptive statistics. All vital signs results will be listed by subject.

7.6 Pulse Oximetry

Pulse oximetry will be performed at the following time points:

Table 7.6 Pulse Oximetry Time Points

Period	Period Day	Study Hour
1	Day 1	0**
1	Day 1	0.5
1	Day 1	0.75
1	Day 1	2
1	Day 1	4
1	Day 1	6
2	Day 10	0**
2	Day 10	0.2
2	Day 10	0.5
2	Day 10	2
2	Day 10	4
2	Day 10	6
* performed within 24 hours prior dosing ** performed prior dosing *** performed at the end of Period 2 or prior to ET		

Descriptive statistics will be reported for pulse oximetry and change from baseline by treatment and time point. Baseline is Day 1 predose of Treatment A (Period 1) and Day 10 predose of Treatment B (Period 2) and is the last non-missing predose measurement prior to dosing of midazolam, including rechecks and unscheduled assessments. Postdose recheck values and ET results will not be used for calculation of descriptive statistics. All pulse oximetry results will be listed by subject.

7.7 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	

Period	Period Day	Study Hour
1	Day -1	Check-in*
1	Day 1	2
2	Day 1	0**
2	Day 1	1.5
2	Day 3	0**
2	Day 4	0**
2	Day 5	0**
2	Day 6	0**
2	Day 7	0**
2	Day 8	0**
2	Day 9	0**
2	Day 9	2
2	Day 10	0**
2	Day 10	2
2	Day 11	24***
* performed within 24 hours prior dosing ** performed prior dosing *** performed at the end of Period 2 or prior to ET		

Descriptive statistics will be reported for ECG parameters and change from baseline by treatment and time point. Baseline is Day -1 of Treatment A (Period 1) and Day 1 predose of Treatment B (Period 2) and is the last non-missing predose measurement prior to dosing of midazolam (Treatment A) or LOXO-292 (Treatment B), including rechecks and unscheduled assessments. Postdose recheck values 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.

7.8 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary, Version Mar2017 B3 and listed.

7.9 Physical Examination

A full physical examination will be performed at screening. Abbreviated physical examinations may be performed at other times, at the PI's or designee's discretion, including Day 1 predose of the second 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 Conference on 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 Midazolam Pharmacokinetic Parameters Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Table 11-3 Summary of Statistical Comparisons of Plasma Midazolam Pharmacokinetic Parameters Following Coadministration of a Single Dose of 2 mg Midazolam with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) Versus Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) (Pharmacokinetic Population)

Table 11-4 Summary of Plasma 1-OH-Midazolam Pharmacokinetic Parameters Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Table 11-5 Summary of Statistical Comparisons of Plasma 1-OH-Midazolam Pharmacokinetic Parameters Following Coadministration of a Single Dose of 2 mg Midazolam with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) Versus Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) (Pharmacokinetic Population)

Table 11-6 Summary of Plasma LOXO-292 Pharmacokinetic Parameters Following Administration of a Single Dose of 160 mg LOXO-292 Alone (Day 1) and Multiple Twice Daily Doses of 160 mg LOXO-292 Alone (Day 9) and Coadministered with a Single Dose of 2 mg Midazolam (Day 10) (Treatment B) (Pharmacokinetic Population)

Table 11-7 Steady-State Assessment of Plasma LOXO-292 Concentrations on Days [redacted] (Pharmacokinetic Population)

Figure 11-1 Arithmetic Mean Plasma Midazolam Concentration-Time Profiles Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Figure 11-2 Arithmetic Mean Plasma 1-OH-Midazolam Concentration-Time Profiles Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Figure 11-3 Arithmetic Mean Plasma LOXO-292 Concentration-Time Profiles Following Administration of a Single Dose of 160 mg LOXO-292 Alone ([redacted]) and Multiple Twice Daily Doses of 160 mg LOXO-292 Alone ([redacted]) and Coadministered with a Single Dose of 2 mg Midazolam ([redacted]) (Treatment B) (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

Table 14.1.1.1 Summary of Disposition (Safety Population)
Table 14.1.1.2 Disposition of Subjects (Safety Population)
Table 14.1.1.3 Demographic Summary (Safety Population)

14.2 Pharmacokinetic Data Summary Tables and Figures

14.2.1 Midazolam and 1-OH-Midazolam

14.2.1.1 Plasma Midazolam and 1-OH-Midazolam Tables

14.2.1.2 Plasma Midazolam and 1-OH-Midazolam Figures

14.2.2 LOXO-292

14.2.2.1 Plasma LOXO-292 Tables

14.2.2.2 Plasma LOXO-292 Figures

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

16.2.3. Subjects Excluded from Pharmacokinetic Analysis

Appendix 16.2.3 Subjects Excluded from Pharmacokinetic Analysis

Note: Appendices 16.2.2 and 16.2.3 are 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 and Return Criteria

16.2.6 Individual Pharmacokinetic Response Data

16.2.7 Adverse Events Listings

16.2.8 Listings of Individual Laboratory Measurements and Other Safety Observations

Appendix 16.2.8.1.1	Clinical Laboratory Report - Serum Chemistry (Safety Population)
Appendix 16.2.8.1.2	Clinical Laboratory Report - Hematology and Coagulation (Safety Population)
Appendix 16.2.8.1.3	Clinical Laboratory Report - Urinalysis (Safety Population)
Appendix 16.2.8.1.4	Clinical Laboratory Report - Urine Drug Screening (Safety Population)
Appendix 16.2.8.1.5	Clinical Laboratory Report - Comments (Safety Population)
Appendix 16.2.8.2	Vital Signs (Safety Population)
Appendix 16.2.8.3	12-Lead Electrocardiogram (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.

10.1 In-text Table Shells

Table 10-1 Summary of Disposition (Safety Population)

Disposition	Treatment		Overall
	A	B	
Enrolled	XX (100%)	XX (100%)	XX (100%)
Completed Study	XX (XX%)	XX (XX%)	XX (XX%)
Discontinued Early	XX (XX%)	XX (XX%)	XX (XX%)
<Reason1>	XX (XX%)	XX (XX%)	XX (XX%)
<Reason2>	XX (XX%)	XX (XX%)	XX (XX%)

Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10

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		**Study Overall**
Sex	Male	XX (XX%)
	Female	XX (XX%)
Race	Asian	XX (XX%)
	Black or African American	XX (XX%)
	White	XX (XX%)
Ethnicity	Hispanic or Latino	XX (XX%)
	Not Hispanic or Latino	XX (XX%)
Age* (yr)	n	XX
	Mean	XX.XX
	SD	XX.XXX
	Minimum	XX.XX
	Median	XX.X
	Maximum	XX.XX
Height (cm)	n	XX
	Mean	XXX.X
	SD	X.XX
	Minimum	XXX
	Median	XXX.X
	Maximum	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, 11-4, and 11-6 will be in the following format:

Table 11-2 Summary of Plasma Midazolam Pharmacokinetic Parameters Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Pharmacokinetic Population)

Pharmacokinetic Parameters	Treatment A	Treatment B
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]
Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1 Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10 AUCs 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 14.2.1.1.5 and 14.2.1.1.8		

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order:
  - Table 11-2 (Midazolam): AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F, and Vz/F
  - Table 11-4 (1-OH Midazolam): AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, and t½
  - Table 11-6 (LOXO-292): 3 columns for Treatment B will be presented: SD LOXO-292 Alone, MD LOXO-292 Alone, MD LOXO-292 Coadministered with Midazolam
    - SD LOXO-292 Alone: AUC0-12, Cmax, Tmax
    - MD LOXO-292 Alone: AUCtau, Cmax,ss, Ctrough (Day 1), Ctrough (Day 2), Ctrough (Day 3), Ctrough (Day 4), Ctrough (Day 5), Ctrough (Day 6), Ctrough (Day 7), Tmax,ss, CL,ss/F, Vz,ss/F
    - MD LOXO-292 Coadministered with Midazolam: AUCtau, Cmax,ss, Tmax,ss, CL,ss/F, Vz,ss/F
- 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
```

In-text Tables 11-3 and 11-5 will be in the following format:

Table 11-3 Summary of Statistical Comparisons of Plasma Midazolam Pharmacokinetic Parameters Following Coadministration of a Single Dose of 2 mg Midazolam with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) Versus Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) (Pharmacokinetic Population)

Parameter	Treatment B (Test)		Treatment A (Reference)		GMR (%)	90% Confidence Interval	Intra-subject CV%
	Geometric LSMs	n	Geometric LSMs	n			
param1 (units)	XXX.X	XX	XXX.X	XX	XX.XX	XX.XX - XX.XX	X.XX
param2 (units)	XXX.X	XX	XXX.X	XX	XX.XX	XX.XX - XX.XX	X.XX
param3 (units)	XXX.X	XX	XXX.X	XX	XX.XX	XX.XX - XX.XX	X.XX

Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10

Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.1.1.11

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order: AUC0-t, AUC0-inf, and Cmax
- n will be presented as an integer (with no decimal);
- All 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
```

In-text Table 11-7 will be in the following format:

Table 11-7 Steady-State Assessment of Plasma LOXO-292 Concentrations on CCI (Pharmacokinetic Population)

Treatment	Days	Geometric LSM	p-value
Treatment B	DAY 7	X.XXX	X.XXXX
	DAY 8	X.XXX	X.XXXX
	DAY 9	X.XXX	X.XXXX

Concentrations were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) were obtained by taking exponential of the LSMs from ANOVA.

P-value corresponds to the Helmert contrast, i.e., the comparison of that day versus the average of the remaining days.
Source: Table 14.2.2.1.3

Notes for Generating the Actual Table:

Presentation of Data:

- Geometric LSM will be presented to precision as in the bioanalytical data +1 decimal place precision
- p-value will be presented to 4 decimals

Please use CPSS1 internal template

Program: DM_PX:[HLXXXXX.PKSAS]STEADYSTATE-HELMERT.SAS
XXAPRXXXX 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	B1	B2	
Number of Subjects Dosed	XX (100%)	XX (100%)	XX (100%)	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 21.0 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: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B1: Multiple doses of 160 mg LOXO-292 BID from Day CCI
Treatment B2: Multiple doses of 160 mg LOXO-292 BID on Day 10 with a single dose of 2 mg midazolam coadministered on the morning of Day 10

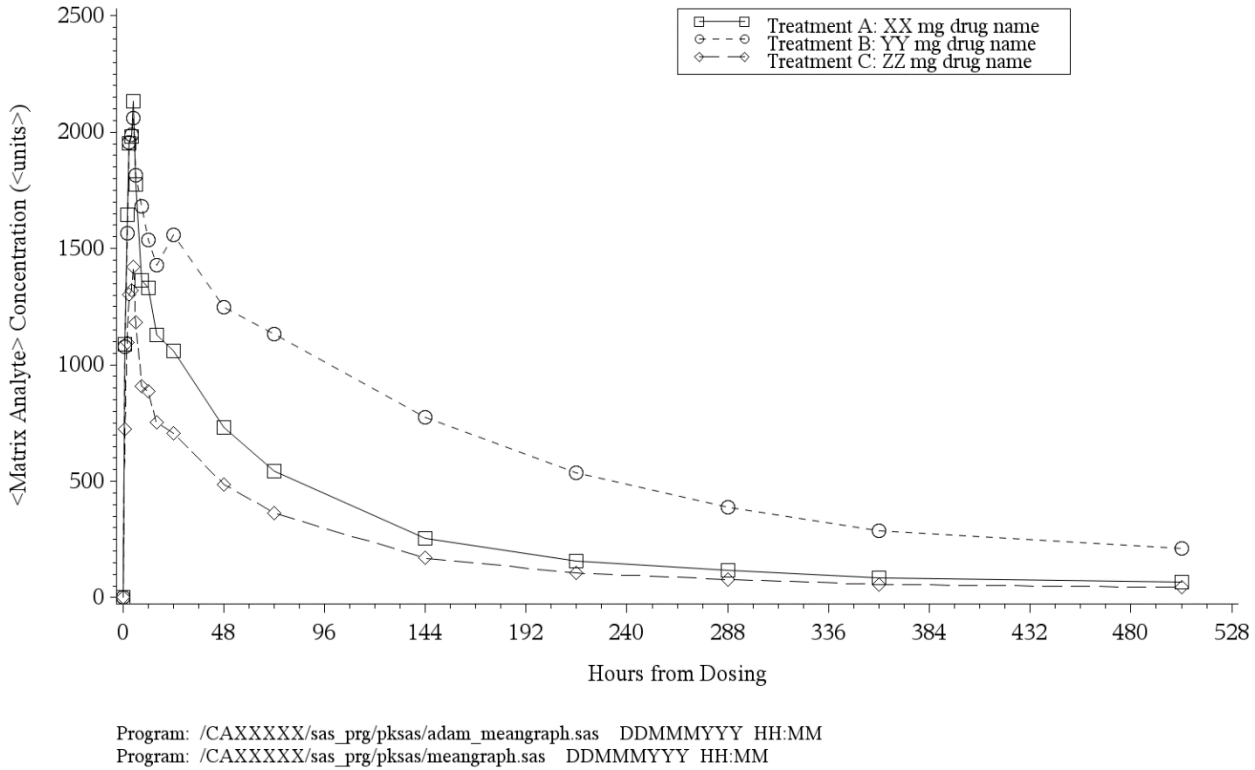
Source: Table 14.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_ae.sas DDMMMYYYY HH:MM

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 through 11-3 and Figures 14.2.1.2.2, 14.2.1.2.5, 14.2.2.2.2, and 14.2.2.2.5 will be in the following format:

Figure 11-1 Arithmetic Mean Plasma Midazolam Concentration-Time Profiles Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Pharmacokinetic Population)



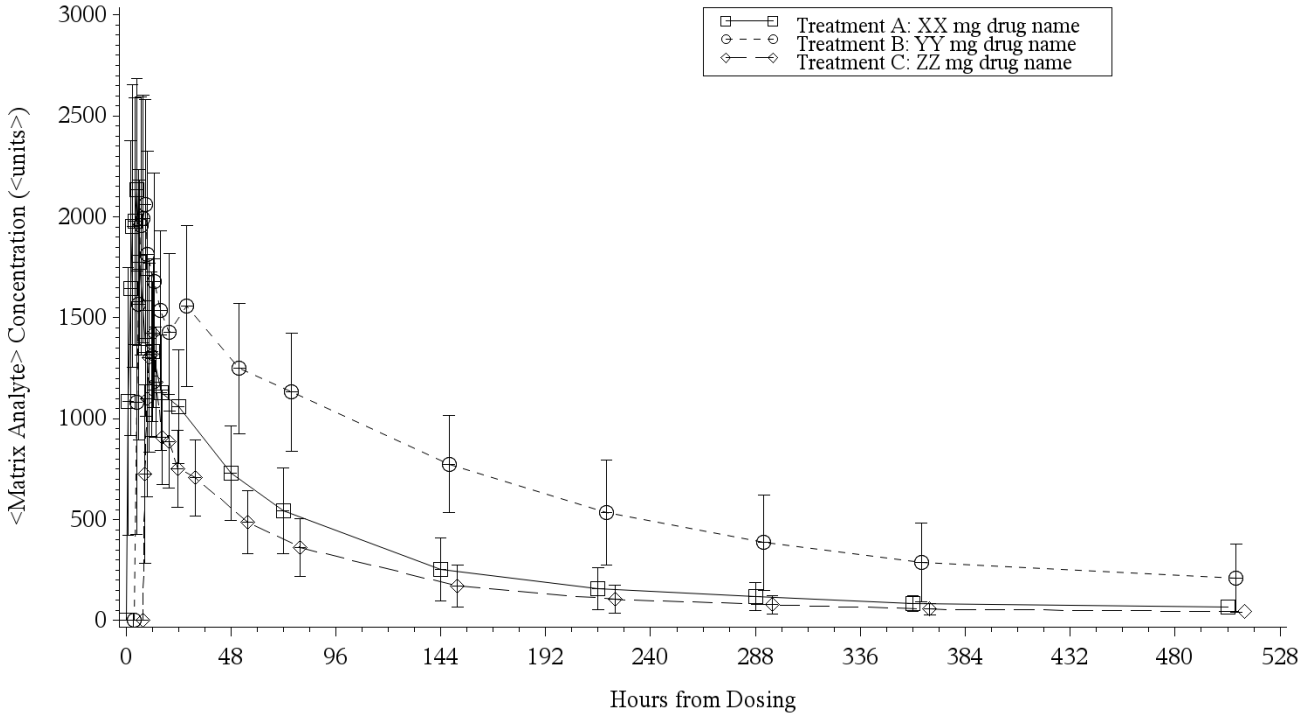
Notes for Generating the Actual Mean Figure:

- Figures 11-1 and 14.2.1.2.2:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Figures 11-2 and 14.2.1.2.5:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma 1-OH-Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Figures 11-3 and 14.2.2.2.2:
  - Legend will be:
    - Single Dose of 160 mg LOXO-292 on CCI
    - Multiple BID Doses of 160 mg LOXO-292 CCI
    - Multiple BID Doses of 160 mg LOXO-292 CCI
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Morning Dose"
- Figure 14.2.2.2.5:
  - Legend will be:
    - Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Trough Day"

```
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, 14.2.1.2.4, 14.2.2.2.1, and 14.2.2.2.4 will be in the following format:

Figure 14.2.1.2.1 Mean (SD) Plasma Midazolam Concentration-Time Profiles Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Linear Scale) (Pharmacokinetic Population)



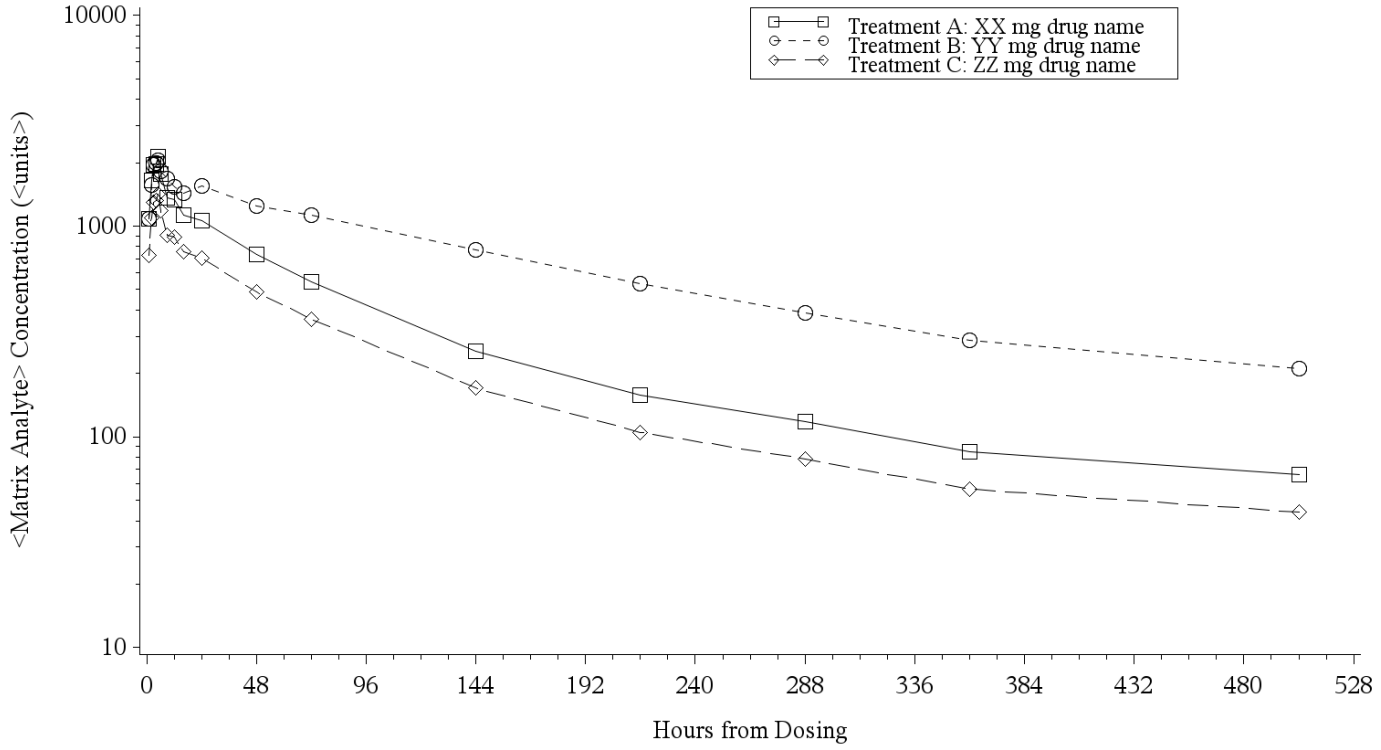
Notes for Generating the Actual Mean Figure:

- Figure 14.2.1.2.1:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Figure 14.2.1.2.4:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma 1-OH-Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Figure 14.2.2.2.1:
  - Legend will be:
    - 160 mg LOXO-292 on Day 1
    - Multiple BID Doses of 160 mg LOXO-292 Day 9
    - Multiple BID Doses of 160 mg LOXO-292 Day 10
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Morning Dose"
- Figure 14.2.2.2.4:
  - Legend will be:
    - Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Trough Day"

```
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, 14.2.1.2.6, and 14.2.2.2.3 will be in the following format:

Figure 14.2.1.2.3 Mean Plasma Midazolam Concentration-Time Profiles Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Semi-Log Scale) (Pharmacokinetic Population)



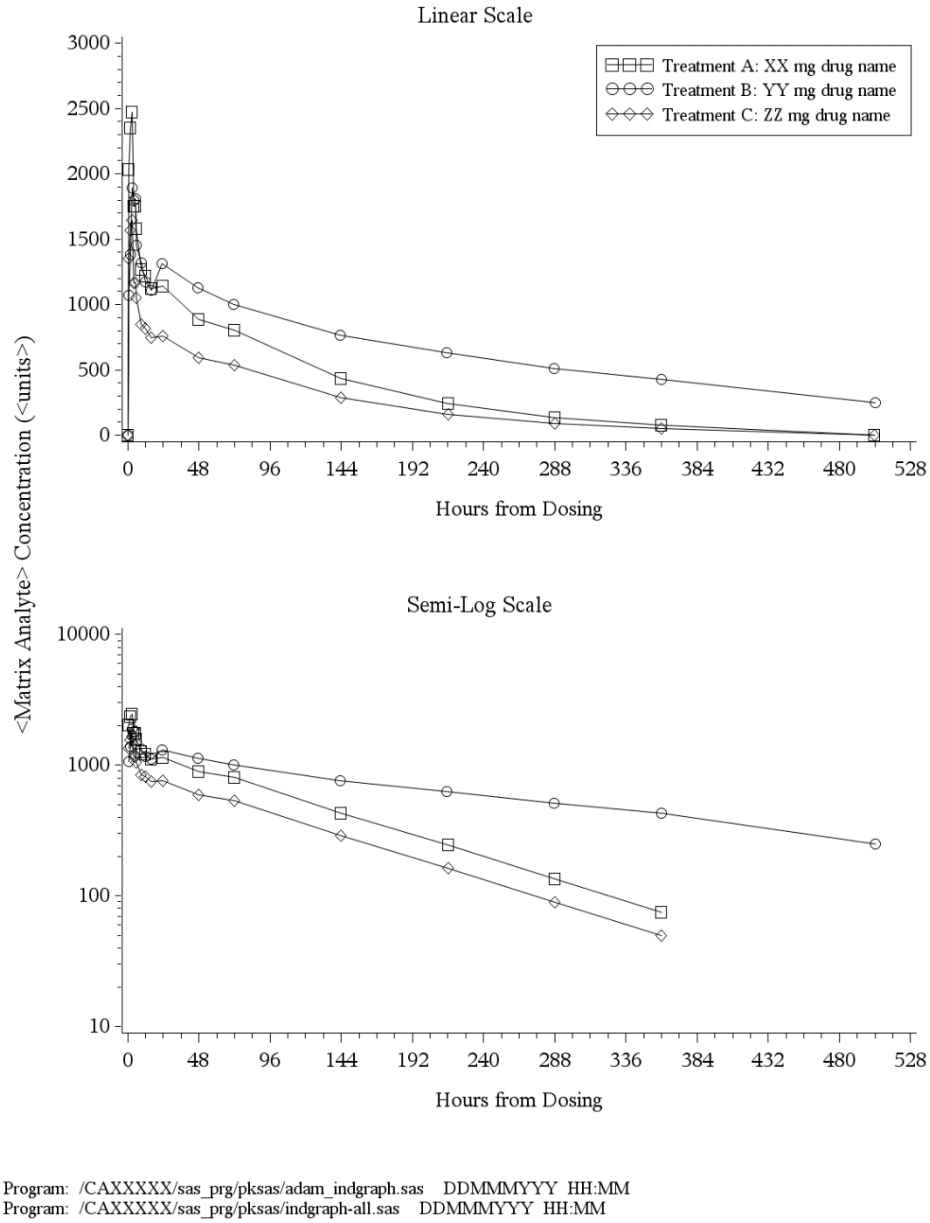
Notes for Generating the Actual Mean Figure:

- Figure 14.2.1.2.3:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Figure 14.2.1.2.6:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma 1-OH-Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Figure 14.2.2.2.3:
  - Legend will be:
    - 160 mg LOXO-292 on Day 1
    - Multiple BID Doses of 160 mg LOXO-292 Day 9
    - Multiple BID Doses of 160 mg LOXO-292 Day 10
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Morning Dose"

```
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 through 16.2.6.3 will be in the following format:

Appendix 16.2.6.1
Individual Plasma Midazolam Concentrations Versus Time Profiles Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) for Subject X (Linear and Semi-Log Scale)



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

Notes for Generating the Actual Individual Figure:

- Appendix 16.2.6.1:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Appendix 16.2.6.2:
  - Legend will be:
    - Treatment A: Administration of a Single Dose of 2 mg Midazolam Alone
    - Treatment B: Coadministration of a Single Dose of 2 mg Midazolam with Multiple BID Doses of 160 mg LOXO-292
  - Y-axis label will be "Plasma 1-OH-Midazolam Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from Midazolam Dose"
- Appendix 16.2.6.3:
  - Legend will be:
    - 160 mg LOXO-292 on Day 1
    - Multiple BID Doses of 160 mg LOXO-292 Day 9
    - Multiple BID Doses of 160 mg LOXO-292 Day 10
  - Y-axis label will be "Plasma LOXO-292 Concentration (ng/mL)"
  - X-axis label will be "Hours Postdose (hr) from LOXO-292 Morning Dose"

```
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)

	Treatment		
Disposition	A	B	Overall
Enrolled	XX	XX	XX
Completed	XX	XX	XX
Discontinued Early	XX	XX	XX
Reason 1	XX	XX	XX
Reason 2	XX	XX	XX
Reason 3	XX	XX	XX
etc.			

Note: Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10

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

Table 14.1.1.2 Disposition of Subjects (Safety Population)

Subject Number	Treatment Sequence	Dosed Period 1	Dosed Period 2	Completed Period 1	Completed Period 2	Study Completion Status	Study Completion Date
XXX-XXX	AB	Yes	Yes	Yes	Yes	Completed Study	DDMMYYYY
XXX-XXX	AB	Yes	Yes	Yes	No	Terminated Study Prematurely	DDMMYYYY

Note: Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10

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

Table 14.1.1.3 Demographic Summary (Safety Population)

Trait		Study Overall
Sex	Male	X (XX%)
	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 through 14.2.1.1.4, and 14.2.2.1.1 through 14.2.2.1.4 will be in the following format:

Table 14.2.1.1.1 Plasma Midazolam Concentrations (ng/mL) Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A)
(Pharmacokinetic Population)

			Sample Times (hr)								
Subject Number	Treatment Sequence	Study Period	Predose	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXX	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:
  - Tables 14.2.1.1.1 through 14.2.1.1.4: CCI [redacted]
  - Table 14.2.2.1.1: CCI [redacted]
  - Table 14.2.2.1.2: CCI [redacted]
  - Table 14.2.2.1.3: CCI [redacted]
  - Table 14.2.2.1.4: CCI [redacted]

Per study design needs, the following changes are made to this table relative to Celerion standard:

1. Please remove the "Treatment Sequence" column

```
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 14.2.1.1.5 through 14.2.1.1.8, and 14.2.2.1.6 through 14.2.2.1.8 will be in the following format:

Table 14.2.1.1.5 Plasma Midazolam Pharmacokinetic Parameters Following Administration of a Single Dose of 2 mg Midazolam Alone (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	XXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	X.XX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	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:
  - Table 14.2.1.1.5 and 14.2.1.1.6: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F, and Vz/F
  - Table 14.2.1.1.7 and 14.2.1.1.8: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, and t½
  - Table 14.2.2.1.6: AUC0-12, Cmax, Tmax
  - Table 14.2.2.1.7: AUCtau, Cmax,ss, Ctrough (Day 1), Ctrough (Day 2), Ctrough (Day 3), Ctrough (Day 4), Ctrough (Day 5), Ctrough (Day 6), Ctrough (Day 7), Tmax,ss, CL,ss/F, Vz,ss/F
  - Table 14.2.2.1.8: AUCtau, Cmax,ss, Tmax,ss, CL,ss/F, Vz,ss/F
- n will be presented as an integer (with no decimal);
- Parameter values for exposure-based parameters (i.e. AUCs, AUC%extrap, Cmax, Ctrough, CL/F, and Vz/F) will be presented with, at maximum, the precision of the bioanalytical data, and, at minimum, 3 significant figures (to be determined by the PKist once the bioanalytical data are received).
  - 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 t1/2) 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
- Remove 'Treatment Sequence'

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

Tables 14.2.1.1.9 and 14.2.2.1.10 will be in the following format:

Table 14.2.1.1.9 Intervals (Hours) Used for Determination of Plasma Midazolam Kel Values Following Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) and Coadministered with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) (Pharmacokinetic Population)
(Pharmacokinetic Population)

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

Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10
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)

Per study design needs, the following changes are made to this table relative to Celerion standard:

1. Remove treatment sequence.

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

Tables 14.2.1.1.11 and 14.2.2.1.12 will be in the following format:

Table 14.2.1.1.11 Statistical Comparisons of Plasma Midazolam Pharmacokinetic Parameters Following Coadministration of a Single Dose of 2 mg Midazolam with Multiple Twice Daily Doses of 160 mg LOXO-292 (Treatment B) Versus Administration of a Single Dose of 2 mg Midazolam Alone (Treatment A) (Pharmacokinetic Population)

				Treatment		Geometric		
		------- Geometric LSMs -------				Mean	90%	Intra-subject
Parameter	(unit)	B	(n)	A	(n)	Ratio	Confidence Intervals	CV%
Param1	(unit)	X.XX	(n)	X.XX	(n)	X.XX	XX.XX - XXX.XX	X.XX
Param2	(unit)	X.XX	(n)	X.XX	(n)	X.XX	XX.XX - XXX.XX	X.XX
Param3	(unit)	X.XX	(n)	X.XX	(n)	X.XX	XX.XX - XXX.XX	X.XX

Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from ANOVA.
Geometric Mean Ratio = 100*(B/A)
Intra-subject CV% = 100 x (square root (exp[MSE]-1), where MSE = Residual variance from ANOVA.

Notes for Generating the Actual Table:

Presentation of Data:

- Geometric LSMs will be presented to the same precision as the Mean in the PK parameter table,
- Geometric Mean Ratio, 90% CI and intra-subject CV% will be presented to 2 decimal places,
- PK parameters to be presented are AUC0-t, AUC0-inf, and Cmax

Program: /CAXXXXX/sas_prg/pksas/stats-tables-mixed.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_statsmixed.sas DDMMMYYYY HH:MM

Table 14.2.2.1.9 will be presented in the following format:

Table 14.2.2.1.9 Steady-State Assessment of Plasma LOXO-292 Concentrations on Days 7 Through 9 (Pharmacokinetic Population)

Treatment	Days	Geometric LSM	p-value
Treatment B	DAY 5	X.XXX	X.XXXX
	DAY 6	X.XXX	X.XXXX
	DAY 7	X.XXX	X.XXXX
	DAY 8	X.XXX	X.XXXX
	DAY 9	X.XXX	X.XXXX

Concentrations were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) were obtained by taking exponential of the LSMs from ANOVA.

P-value corresponds to the Helmert contrast, i.e., the comparison of that day versus the average of the remaining days.

Notes for Generating the Actual Table:

Presentation of Data:

- Geometric LSM will be presented to the same precision as the bioanalytical data +1 decimal place precision
- p-value will be presented to 4 decimals

Programmer Note: Please use Table CPSS1 internal template

Notes for preparation of standard programs (to be deleted after standard programs are updated):
Update standard program name to include CPSS1 shell name

Program: DM_PX:[HLXXXXX.PKSAS]STEADYSTATE-HELMERT.SAS XXAPRXXXX 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	B1	B2	Overall
Number of Subjects Dosed	X (100%)	X (100%)	X(100%)	X(100%)
Number of Subjects with TE Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)
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 21.0 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: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B1: Multiple doses of 160 mg LOXO-292 BID from Day [redacted]
Treatment B2: Multiple doses of 160 mg LOXO-292 BID on Day 10 [redacted] ngle dose of 2 mg midazolam coadministered on the morning of Day 10

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 – Number of Adverse Events (% of Total Adverse Events) (Safety Population)

	Treatment			
TE Adverse Event*	A	B1	B2	Overall
Number of TE Adverse Events	X (100%)	X (100%)	X(100%)	X(100%)
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 theMedDRAthe MedDRA Version 21.0 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 X: <description>

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.

Table 14.3.1.3 Treatment-Emergent Adverse Event Frequency by Treatment, Severity Grade, and Relationship to Study Drugs - Number of Subjects Reporting Events (Safety Population)

TE Adverse Event*	Treatment	Number of Subjects with Adverse Events	Severity Grade					Relationship to LOXO-292		Relationship to Midazolam	
			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	B1	X	X	X	X	X	X	X	X	X	X
Dry mouth	A	X	X	X	X	X	X	X	X	X	X
	B1	X	X	X	X	X	X	X	X	X	X
Dry throat	B1	X	X	X	X	X	X	X	X	X	X
Ear pain	A	X	X	X	X	X	X	X	X	X	X
Fatigue	B2	X	X	X	X	X	X	X	X	X	X
Treatment A		XX	X	X	X	X	X	X	X	X	X
Treatment B1		XX	X	X	X	X	X	X	X	X	X
Treatment B2		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 21.0 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 X: <description>

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

Table 14.3.1.4 Treatment-Emergent Adverse Event Frequency by Treatment, Severity Grade, and Relationship to Study Drugs - Number of Adverse Events (Safety Population)

			Severity Grade					Relationship to LOXO-292		Relationship to Midazolam	
TE Adverse Event*	Treat-ment	Number of Adverse Events	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	B1	X	X	X	X	X	X	X	X	X	X
Dry mouth	A	X	X	X	X	X	X	X	X	X	X
	B1	X	X	X	X	X	X	X	X	X	X
Dry throat	B1	X	X	X	X	X	X	X	X	X	X
Ear pain	A	X	X	X	X	X	X	X	X	X	X
Fatigue	B2	X	X	X	X	X	X	X	X	X	X
Treatment A		XX	X	X	X	X	X	X	X	X	X
Treatment B1		XX	X	X	X	X	X	X	X	X	X
Treatment B2		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 21.0. 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.
Treatment X: <description>

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	Ser*	Outcome	Action for LOXO-292/ Midazolam	Relationship to LOXO-292/ Midazolam
XXX-XXX	X	Yes	XXXXXXX	XXXXXXX/ XXXXXXXX	XX/ XX	DDMMMYYYY/ DDMMMYYYY	XX:XX/ XX:XX	Inter.	X	NS	Resolved	XXXXXXXXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXXX

Note: * Adverse events are classified according to MedDRA Version 21.0 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
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.
Treatment X: <description>

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	Hour	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)
XXX-XXX	XX/M	Screen			DDMMMYYYY	XX HN G1	XX	XX	XX	XX HN
		1	-X	Check-in	DDMMMYYYY	XX	XX	XX	XX	XX
		2	X	0	DDMMMYYYY	XX	XX	XX	XX HN	XX
			X	0	DDMMMYYYY	XX	XX	XX	XX	XX
			X	0	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.

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, R = To be Rechecked, ^ = Will be Retested at a Later Event
Flag starting with "G" is graded according to NCI CTCAE grading.

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	Hour	Date	Time	Department	Test	Result	Reference Range	Unit
XXX-XXX	XX/X	X	X	X.XX	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX	X – X	mg/dL
			X	XX.XX	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX HYR+G3	X – X	mg/dL
			X	XX.XX	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX HY- G2	X – X	mg/dL
			X	XX.XX	DDMMMYYYY	HH:MM:SS	Serum Chemistry	Cholesterol	XXX HN G1	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 or comment 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
Flag starting with "G" is graded according to NCI CTCAE grading.

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.

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

Laboratory Test (unit)	Normal Range#	Time Point	Statistic	Treatment A	Treatment B	Change From Baseline A	Change From Baseline B
Parameter1 (unit)	XX – XX	Day -1/1$	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 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. Also need to add Days 9 and 11 time points of Period 2 (Treatment B). 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.
$ Day -1 for Treatment A (Period 1) and Day 1 for Treatment B (Period 2)
Baseline is Day 1 predose of Period 2 and is the last non-missing predose measurement prior to dosing of LOXO-292, including rechecks and unscheduled assessments.
Treatment A: <description>
Treatment B: <description>

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.

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

Laboratory Test (units)	Treat-ment	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)	B	Day 3	X	XX	X	X	XX	X	X	XX	X
		Day 6	X	XX	X	X	XX	X	X	XX	X
		Day 9	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 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 predose of Period 2 and is the last non-missing predose measurement prior to dosing of LOXO-292, including Rechecks and unscheduled assessments.
Treatment A: <description>
Treatment B: <description>

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)

		Treatment A			Treatment B		
Vital Sign Parameter (unit)	Statistic	Time Point	Measured Value	Change From Baseline	Time Point	Measured Value	Change From Baseline
Parameter1 (unit)	n	Day -1 Check-in	XX		Day 1 Hour 0	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	
	n	Day 1 Hour 0.75	XX	XX	Day 1 Hour 1.5	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
	n	Day 1 Hour 2	XX	XX	Day 3 Hour 0	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
	n	Day 1 Hour 4	XX	XX	Day 4 Hour 0	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

CCI [redacted]A (Period 1) and Day 1 predose of Treatment B (Period 2) and is the last non-missing predose measurement prior to dosing of midazolam (Treatment A) or LOXO-292 (Treatment B), including rechecks and unscheduled assessments. For respiration rate of Treatment B (Period 2), Day 9 predose is the baseline.>

Treatment A: <description>

Treatment B: <description>

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

Table 14.3.5.8 Pulse Oximetry Summary and Change from Baseline (Safety Population)

		Treatment A			Treatment B		
Parameter (unit)	Statistic	Time Point	Measured Value	Change From Baseline	Time Point	Measured Value	Change From Baseline
Oxygen (%)	n	Day 1 Hour 0	XX		Day 10 Hour 0	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	
	n	Day 1 Hour 0.5	XX	XX	Day 10 Hour 0.2	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
	n	Day 1 Hour 0.75	XX	XX	Day 10 Hour 0.5	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
	n	Day 1 Hour 2	XX	XX	Day 10 Hour 2	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

CCI [redacted] 2) and is the last non-missing predose measurement prior to dosing of midazolam, including rechecks and unscheduled assessments.

Treatment A: <description>
Treatment B: <description>
Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.9 12-Lead Electrocardiogram Summary and Change from Baseline (Safety Population)

ECG Parameter (unit)	Statistic	Treatment A: Time Point	Treatment A: Measured Value	Treatment A: Change From Baseline	Treatment B: Time Point	Treatment B: Measured Value	Treatment B: Change From Baseline
Parameter1 (unit)	n	Day -1 Check-in	XX		Day 1 Hour 0	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	
	n	Day 1 Hour 2	XX	XX	Day 1 Hour 1.5	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
					Day 3 Hour 0	XX	XX
						XX.XX	XX.XX
						X.XXX	X.XXX
						XX.X	XX.X
						XX.XX	XX.XX
						XX.X	XX.X
					Day 4 Hour 0	XX	XX
						XX.XX	XX.XX
						X.XXX	X.XXX
						XX.X	XX.X
						XX.XX	XX.XX
						XX.X	XX.X

CCI [redacted]

predose measurement prior to dosing of midazolam (Treatment A) or LOXO-292 (Treatment B), including rechecks and unscheduled assessments.
Treatment A: <description>
Treatment B: <description>
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.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Normal 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	Treatment Sequence	Study Period	Date	Completed Study?	Primary Discontinuation Reason
XXX-XXX	XX	Post	DDMMMYYYY	YES	
XXX-XXX	XX	Post	DDMMMYYYY	YES	
XXX-XXX	XX	Post	DDMMMYYYY	YES	
XXX-XXX	XX	Post	DDMMMYYYY	YES	
XXX-XXX	XX	Post	DDMMMYYYY	NO	Adverse Event
XXX-XXX	XX	Post	DDMMMYYYY	YES	
XXX-XXX	XX	Post	DDMMMYYYY	YES	
XXX-XXX	XX	Post	DDMMMYYYY	YES	

Note: Treatment A: A single dose of 2 mg midazolam (1 mL of 2 mg/mL syrup) administered at Hour 0 on Day 1
Treatment B: Multiple doses of 160 mg LOXO-292 (2 x 80 mg capsules) administered BID, approximately every 12 hours, for 10 consecutive days with 2 mg midazolam (1 mL of 2 mg/mL syrup) coadministered on the morning of Day 10

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

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 Check-in	DDMMMYYYY	Was PE performed?	Yes	
					HEENT	Unchanged	
					< >	< >	

Note: Treatment A: <description>
Treatment B: <description>

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 Start	Date End	Ongoing?	Condition or Events
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

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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

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Appendix 16.2.5.1.2 Exclusion Criteria

1. Is mentally of 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: <description>
Treatment B: <description>

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

Appendix 16.2.5.4.1 Test Compound Description

Compound	Form	Route
XXXXXXXXXXXXX	< >	XXXX
XXXXXXXXXXXXX	< >	XXXX

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	Date	Actual Time	Compound	Dosage	Comments
XXX-XXX	1	X	X	0	DDMMMYYYY	X:XX:XX	XXXXXXXXX	< >	<This column prints only
	2	X	X	0	DDMMMYYYY	X:XX:XX	XXXXXXXXX	< >	if data is present>

Note: Treatment A: <description>
Treatment B: <description>

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: <description>
Treatment B: <description>

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

Appendix 16.2.5.6 Phone Call (Safety Population)

Subject Number	Study Period	Was a Telephone Call Performed? (Yes/No)	Day	Date	Time	If No, Reason*
XXX-XXX	2	YES	XX	DDMMMYYYY	HH:MM	XXXXXXXXXXXXX

Note: * Reason options: 3 call attempts with no subject return call; Phone Disconnected; Wrong Number

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

Appendix 16.2.5.7 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: <description>
Treatment B: <description>

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

Appendix 16.2.5.8 Prior and Concomitant Medications (Safety Population)

Subject Number	Treat-ment	Any Med^?	Prior to Study?	Medication (WHO* Term)	Dosage	Route	Frequency	Start Day/Date/Time	Stop Day/Date/Time	Indi-cation	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 Mar2017 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: <description>
Treatment B1: <description>
Treatment B2: <description>

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 21.0 by System Organ Class and Preferred Term.
^ TE = Treatment-emergent, Onset and resolved day is relative to Period 1 Day 1.
Treatment A: <description>
Treatment B1: <description>
Treatment B2: <description>

Program: /CAXXXXX/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/ Midazolam	Other Action Taken	Relationship to LOXO-292/ Midazolam
XXX-XXX		None										
XXX-XXX	X	XXXXXXX	XX	DDMMMYYYY	XX:XX	Inter.	Grade 1	NS	Resolved	Dose Not Changed/ Dose Not Changed	XXXXXXXX	Not Related to LOXO-292/ Not Related to Midazolam

Note: Ser* represents Serious: NS = Not 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: <description>
Treatment B1: <description>
Treatment B2: <description>

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: <description>
Treatment B1: <description>
Treatment B2: <description>

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 21.0 by System Organ Class and Preferred Term.
Onset day is relative to Period 1 Day 1.
Treatment A: <description>
Treatment B1: <description>
Treatment B2: <description>

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	Study Period	Day	Hour	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)
XXX-XXX	XX/M	Screen			DDMMMYYYY	XX HN G1	XX	XX	XX	XX HN
		1	-X	Check-in	DDMMMYYYY	XX	XX	XX	XX	XX
		2	X	0	DDMMMYYYY	XX	XX	XX	XX HN	XX
			X	0	DDMMMYYYY	XX	XX	XX	XX	XX
			X	0	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.

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
Flag starting with "G" is graded according to NCI CTCAE grading.

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	Study Period	Day	Hour	Date	Department	Test	Result	Unit	Comment
XXX-XXX	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	Treatment	Day	Hour	Date	Time	Blood Pressure (mmHg) Test	Arm	Sys/Dia	Pulse (bpm)	Respiration (rpm)	Temperature (°C)	Oxygen (%)	Weight (kg)	Comments
XXX-XXX	Screen				DDMMMYYYY	X:XX:XX								XXX.X	
					DDMMMYYYY	X:XX:XX	SITX	Right	XXX/ XX	XX	XX	XX.X			
	X	X	-X	Check-in	DDMMMYYYY	XX:XX:XX								XXX.X	
					DDMMMYYYY	XX:XX:XX	SITX	Right	XXX/ XX	XX	XX				
			X	X.X	DDMMMYYYY	XX:XX:XX	SITX	Right					XX		
				X.X	DDMMMYYYY	XX:XX:XX	SITX	Right					XX		
				X.X	DDMMMYYYY	X:XX:XX	SITX	Right	XXX/ XX	XX	XX		XX		
				X.X	DDMMMYYYY	X:XX:XX	SITX	Right	XXX/ XX	XX	XX		XX		
				X.X	DDMMMYYYY	X:XX:XX	SITX	Right	XXX/ XX	XX	XX		XX		
				R	DDMMMYYYY	XX:XX:XX	SITX	Right	XXX/ XX	XX	XX				
				X.X	DDMMMYYYY	XX:XX:XX	SITX	Right					XX		

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: SITX = X-minute sitting, R = Recheck Value, Sys/Dia = Systolic/Diastolic
Treatment A: <description>
Treatment B: <description>

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	X	Check-in	DDMMMYYYY	X:XX:XX	ANCS	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	ANCS	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: ANCS = Abnormal, Not Clinically Significant
QTcF* = QT corrected for heart rate using Fridericia's correction.
= QTcF > 450, @ = QTcF change from baseline greater than 30 msec
Treatment A: <description>
Treatment B: <description>

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