Statistical Analysis Plan: J2D-MC-CVAC (v1)

A Safety, Tolerability and Pharmacokinetic Study of Single and Multiple Doses of LY3526318 in Healthy Participants

NCT04682119

Approval Date: 22-Apr-2021

Statistical Analysis Plan

Sponsor:	Eli Lilly and Company
Protocol No:	J2D-MC-CVAC (c)
Protocol Title:	A Safety, Tolerability, Pharmacokinetic Study of Single and Multiple Doses of LY3526318 in Healthy Participants
PRA Project ID:	CHO20244-20244X
Version Date:	22-Apr-2021 (SAP)

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative/ Title:	PPD
Signature of Sponsor Representative/ Date:	
Name of Sponsor Representative/ Title:	
Signature of Sponsor Representative/ Date:	
Name of Author/ Title:	PPD
Signature of Author/ Date:	

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Eli Lilly and Company Protocol J2D-MC-CVAC.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the SAP has been developed using the protocol dated 11-Mar-2021 (including all amendments up to this protocol date) and the final eCRF(s): SAD V1 dated 22Jan21, SAD V2 dated 12-Mar-2021 and MAD V1 dated29-Mar-2021.

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the pharmacokinetic (PK), and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

The study objectives are given in Table 1 below.

Table 1 Objectives and Endpoints.

Objective	Endpoints
Primary (Part A -SAD)	
• To determine the pharmacokinetics of LY3526318 after a single oral dose administration	• AUC • C_{max}
Primary (Part B -MD)	
• To determine the pharmacokinetics of LY3526318 after multiple oral dose administrations	• AUC • C_{max}
Secondary (Part A – SAD)	
• To estimate the safety and tolerability of LY3526318 af ter single oral administration to healthy participants • To evaluate the effect of a meal on the pharmacokinetics of LY3526318 in fed versus fasted conditions	• AEs • SAEs • C_{max} • T_{max} • AUC
Secondary (Part B – MD)	
• To estimate the safety and tolerability of LY3526318 af ter multiple oral administration to healthy participants	• AEs • SAEs

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; MD = multiple dose; SAD = single-ascen ding dose; SAE = serious adverse event; T_{max} = time to C_{max}

6.0 Study Design

This is a Phase 1, randomized, double-blind and placebo-controlled single ascending dose (SAD, Part A) and multiple dose (MD, Part B) study of LY3526318 in healthy participants. A maximum of 16 participants (SAD and MD cohorts, size of 8) will be enrolled.

Part A (SAD):

A single cohort of 8 healthy participants will be randomized to a sequence in which LY3526318 or placebo will be administered in a 3:1 ratio. In each dosing period, different participants will receive placebo. In this adaptive dose study, subsequent dose levels will be selected based on saf ety and PK. Doses will be selected to maintain geometric mean $AUC_{0\text{-}inf}$ below the lowest no-observed-adverse-effect level (NOAEL) from animal toxicology studies (154 µg.h/mL).

Of the 4 treatment periods planned for Part A, up to 3 single dose levels will be assessed in a f asted state (f asting at least 8 hours prior to and at least 4 hours after dosing). Up to two of these dose levels that were assessed in a f asted state may also be assessed in a f ed state (a high-f at meal or a light breakfast 30 minutes prior to dosing).

Randomized to Treatment/Sequence:

Treatment	SAD Periods [N=8]			
Sequence [n]	A1 (f asted)	A2 (f asted)	A3 (f ed)	A4 (f ed)
1 [2]	P	L2	L3	L4
2 [2]	L1	P	L3	L4
3 [2]	L1	L2	P	L4
4 [2]	L1	L2	L3	P

Single doses are L1, L2, L3, L4, P (Placebo); L = level of dose (mg);
Abbreviations: N = number of participants; n = number of participants in specific population; SAD = single ascending dose.

Following a screening period of up to 28 days, eligible participants will be confined to the clinical research unit (CRU) from Day -1 until all study assessments are completed on Day 3. All participants will return to the CRU after the last study period for a final visit on Day 10.

Part B (MD):

After a dose is identified from Part A, multiple doses of LY3526318 or placebo will be administered for up to 5 days. Eight treatment-naïve participants will be randomized to receive LY3526318 or placebo in a 3:1 ratio. Additional participants will be enrolled for a total cohort size of 8 completers. Part B will involve dosing in a f asted or f ed state (e.g., standard meal or a light breakfast as described in site-specific manual) depending on the results from Part A. The dose regimen and fed/fasting will be selected with the intent not to exceed the AUC_{0-24} achieved in Part A. Part B is not designed to assess the impact of food on exposure.

Randomized to Treatment/Sequence:

Treatment	MD [N=8]
Sequence [n]	B
5 [6]	LX
5 [2]	P

Multiple Dose (MD) is dose LX that is ≤ single dose
Abbreviations: N = number of participants; n = number of participants in specific population; P = placebo.

Participants will be confined to the CRU from Day -1 until all study assessments are completed 72 hours after the last dose. Participants will return to the CRU for a final visit on approximately Day 14.

6.1 Sample Size Considerations

A maximum of 16 participants (SAD and MD cohorts of size 8, randomized 3:1) will be randomly assigned to study intervention such that approximately 16 evaluable participants complete the study.

6.2 Randomization

A randomization schedule will be prepared by the Biostatistics Department of PRA. Eight participants (numbered 101-108) will be assigned to one of the 4 sequences in Part A and 8 participants (numbered 201-208) will be assigned to Part B.
Replacement participants will receive the same randomization number as the participant to be replaced increased by 1000 and will be administered the same treatment (sequence).

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from the protocol.

7.2 Interim Analysis and Key Results

Blinded interim PK reports will be provided by the Biostatistics Department of PRA EDS after completion of each dose level. These reports will be created from blinded concentration data versus scheduled time provided by the PRA bioanalytical laboratory.

7.3 Final Analysis

Draft tables, figures, and listings (TFLs) will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the first draft CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all safety summaries except PK data summaries, descriptive statistics will be presented with the same precision (same number of decimals or significant figures) as the data they are calculated from. Frequency percentages will be presented as integers.

For all PK data (i.e. concentrations and derived parameters) summaries, descriptive statistics will be presented as integers when values are ≥100 or presented with 3 significant digits when values are <100. Ratios will be presented with 2 decimals. The T_{max} values and descriptive statistics thereof will be reported with 2 decimals. The coefficient of variation (CV%) will be reported with 1 decimal.

Any p-values will be reported to 4 decimal places; p-value less than 0.0001 will be reported as p <0.0001.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), minimum value, median, and maximum value.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of participants exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the eCRF/Database.

9.1.4 Pooling

Summary statistics will be calculated by study part, treatment (and time point, if applicable). Placebo data will be pooled for Part A (SAD). Placebo data from the periods under fed conditions (i.e. Periods 3 and 4 for Part A) will be reported as a separate treatment for each meal condition.

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations within each period is defined as the last observation recorded before the first study drug administration in each period. The last observation can be an unscheduled/repeated measurement. If a pre-treatment observation is missing in a given period then the screening value may be used.

In case of triplicate electrocardiogram (ECG) assessments, baseline is defined as the mean of the last recorded triplicate before the first study drug administration in each period. If no triplicate is available before the first study drug administration, the mean of the last recorded duplicate closest to the first study drug administration will be considered as baseline. If no triplicate or duplicate is available, the last single ECG recorded before the first study drug administration will be considered as baseline.

9.2.2 Treatment/Participant Grouping

Label	Grouping
Study Drug	Placebo LY3526318
Study Part / Cohort	Part A: Cohort 1 Part B: Cohort 2
Treatments	Part A (SAD): Placebo (fasted) Placebo (fed, light breakfast) Placebo (fed, high fat) Period 1: 100 mg LY (fasted) Period 2: 250 mg LY (fasted) Period 3: 250 mg LY (fed, light breakfast) Period 4: 250 mg LY (fed, high fat) Part B (MD): Placebo QD 250 mg LY QD

MD = multiple dose; QD = once daily; SAD = single ascending dose.

9.2.3 Common Variable Derivations

Variable	Definition/Calculation	Variable Name*
Change from Baseline	Post-dose observation minus baseline observation	CHG
Analysis Study Day (saf ety data)	Prior to first day of dosing: Date of measurement minus dose date On or after first day of dosing: Date of measurement minus dose date +1	ADY
Scheduled time	Planned time of the assessment. Time in hours of the assessment relative to the planned time of the first drug administration per period.	ATPT/ATPTN
Actual Time	Actual time in hours calculated as the sampling data/time minus the date/time of the first drug administration per period.	ARELTM

*) CDISC ADaM defined variable name

9.2.4 QC

The Analysis Data Model (ADaM) compliant analysis datasets and the TFLs will be QC'd according to the general PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary objective of this study is to characterize the PK the datasets considered critical are subject level, and PK (ADSL, ADPC, and ADPP). As these are related to the primary objectives these datasets will be double programmed per the QC plan.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) ADaM Version 2.1.

The following datasets will be generated:

- Subject Level Analysis Dataset (ADSL)
- Adverse Events Analysis Dataset (ADAE)
- Laboratory Analysis Dataset (ADLB)
- Vital Signs Analysis Dataset (ADVS)
- ECG Analysis Dataset (ADEG)
- PK Concentrations Analysis Dataset (ADPC)
- PK Parameter Analysis Dataset (ADPP)

ADaM compliant datasets will be delivered to the Sponsor. A def ine.xml f ile Version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® Version 8.1 or higher (Certara, Inc.). Additional PK computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned. PK concentrations that appear to be outliers will be assessed on a case-by-case basis.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the PRA EDS–ICH E3 compliant–Abbreviated CSR Template. The layout of TFLs will be according to the PRA EDS standards. No table shells will be provided. The TFLs will be provided in Adobe PDF format.

Format:

- Page size: LETTER.
- Data in listings will be sorted by study part, subject number, period and time point.
- Data In tables will be sorted by study part, treatment and time point. For assessments with multiple time points the treatment and time point will be presented in a column (one column for treatment and one column for scheduled time), other tables may be presented with one column f or each treatment label per part (e.g. AEs and demographic characteristics).
- Column titles will be in title case letters.
- All tables and listings will be in landscape format.
- The treatment labels will be as outlined in Section 9.2.2.

10.0 Analysis Sets

Analyses	Entered/Enrolled Set	Safety Set	Pharmacokinetic Set
Disposition Summaries	✓		
Safety Assessments		✓	
Baseline Characteristics		✓	
Primary Analysis			✓
PK Concentrations			✓
PK Parameters			✓

10.1 Enrolled Set

The enrolled set will consist of all participants who sign the informed consent form. This set will be used for disposition summaries.

10.2 Safety Set

The safety set will consist of all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. This set will be used for the safety data summaries and baseline characteristic summaries.

10.3 Pharmacokinetic Set

The PK set will consist of all participants who received at least 1 dose of LY3526318 and have at least 1 post baseline evaluable PK sample.

Participants who received a dose of LY3526318 and have evaluable PK parameters will be used for the PK analyses.

11.0 Participant Disposition

The number and percentage of participants randomized, dosed (in each period), and members of each analysis set will be presented. The number and percentage of participants who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented. The denominator is the number of subjects randomized.

All disposition data will be listed. All participants who discontinue from the study will be identified.

12.0 Protocol Deviations and Violations

Protocol deviations/violations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

All demographic data as collected during the screenings visit will be listed by participant.

Participant demographics will be summarized descriptively for all participants by study part. The summary will include the participants' age (in years), gender, race, ethnicity, weight (in kg), height (in cm), and body mass index (BMI) (in kg/m^2). Subjects' age will also be presented in categories (18-64 years and >=65 years). Demographics will be summarized for the safety and PK sets.

13.2 Medical History

Medical history will be listed.

13.3 Other Baseline Characteristics

The results of drug and alcohol screen at screening and admission will be listed.

Serology (Hepatitis B surface antigen, Hepatitis C antibody and HIV) at screening will be listed.

The results of pregnancy tests at screening, admission and at the end of the study will be listed.

All SARS-CoV-2 test results will be listed.

14.0 Concomitant Medications

Concomitant medication will be listed by participant. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be identified as such in the listing. If a partial date allows a medication to be considered concomitant it will be categorized as such.

Concomitant medications will be coded according to the World Health Organization–Drug Dictionary Enhanced (WHO-DDE) (version as per the Dictionary Coding Conventions).

15.0 Treatment Compliance and Exposure

All exposure data will be listed by participant.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

16.1.1 Plasma Variables

16.1.1.1 Concentrations

- Plasma concentration of LY3526318
- Plasma concentration of LSN3528305

16.1.1.2 Parameters

- Plasma PK parameters for LY3526318 as defined in Table 2
- Plasma PK parameters for LSN3528305 as defined in Table 2

Table 2: Plasma PK Parameters

Parameter	Description	SAD	MD Day 1	MD Day 5	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.	✓	✓	✓	Cmax f rom WNL
T_{max}	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in hours (h).	✓	✓	✓	Tmax f rom WNL
AUC_{0-t}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	✓			AUClast f rom WNL
AUC_{0-inf}	Area under the plasma concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 20% is required to obtain a reliable AUC_{0-inf}.	✓			AUCINF_obs from WNL If AUC_%Extrap_obs >20% then parameter is flagged
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24 hours post-dose.	✓			AUC0-24 f rom WNL where partial time =24h, if missing for a participant then AUC at nominal time 24h f rom summary file is used for AUC_{0-24}
AUC_{0-tau}	Area under the plasma concentration-time curve over the dosing interval (time 0 to 24h) at steady state.		✓	✓	AUCtau f rom WNL where tau is equal to 24h, if missing for a participant then AUC at nominal time 24h f rom summary file is used for AUC_{0-tau}
λ_z	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least 3 points and an adjusted r^2 greater than 0.80 are required to obtain a reliable λ_z.	✓		✓	Lambda_z from WNL If Rsq adjusted ≤ .80 then parameter is flagged
$t_{1/2}$	Terminal phase half -life expressed in hour (h). Percent extrapolation less than or equal to 20% and adjusted r^2 greater than 0.80 is required to obtain a reliable $t_{1/2}$.	✓		✓	HL_Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq adjusted ≤0.80 then parameter is flagged

Parameter	Description	SAD	MD Day 1	MD Day 5	SAS Programming Notes
CL/F	Apparent oral clearance, calculated as Dose/$AUC_{0\text{-}inf}$ for SAD regimens or Dose/$AUC_{0\text{-}tau}$ for the MAD regimen on Day 5; LY3526318 only	✓		✓	CL_F_obs or CLss_F from WNL respectively. If AUC_%Extrap_obs >20% or Rsq adjusted ≤ 0.80 then parameter is flagged
V_z/F	Apparent volume of distribution calculated as (CL/F)/ λ_z; LY3526318 only	✓			Vz_F_obs from WNL If AUC_%Extrap_obs >20% or Rsq adjusted ≤ 0.80 then parameter is flagged
V_{ss}/F	Apparent volume of distribution at steady state, calculated as CL/F*MRT			✓	Vss_F_obs from WNL
AR_{AUC}	Accumulation ratio $AUC_{0\text{-}tau}$			✓	$AUC_{0\text{-}tau}$ (Day 5)/$AUC_{0\text{-}tau}$ (Day 1), calculated in SAS

Note: AUCs will be calculated using linear up/log down, expressed in units of concentration x time.

MD = multiple dose; SAD = single ascending dose; WNL = WinNonlin.

*) In end-of-text TFLs, subscript will not be used.

All of the flagged parameters will be listed and will be includ ed in the descriptive summaries and all statistical comparisons.

16.2 Pharmacokinetic Summaries

16.2.1 Pharmacokinetic Concentrations

Plasma concentrations for LY3526318 and LSN3528305 below the quantifiable limit (BQL) will be set to ½ lower limit of quantification (LLOQ) in the computation of mean concentration values. Descriptive statistics (number of participants, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean and geometric CV%) will be used to summarize the plasma concentrations by treatment at each scheduled time point. If over ½ of the participants in a given cell have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and minimum. With the exception of maximum, all other statistics will be missing.

Linear and semi-logarithmic plots of the geometric mean plasma concentration by scheduled sampling time will be presented by study part and treatment for each analyte separately. These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given time point if more than half of the participants have values BQL.

The SAD treatments will be presented in one plot. Separate plots will be provided for food effect results. The full profile of the MD treatment will be presented in one plot from Day 1 to the last scheduled time point). In addition, an overlay plot for the MD treatment will be presented, showing Day 1 and Day 5 in one plot.

Linear and semi-logarithmic plots of the combined individual plasma concentrations by actual sampling times will be provided by treatment for each analyte (one treatment per page). For the MD Part, the full profiles will be presented. These plots will show time in hours and will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

Linear and semi-logarithmic plots of the individual plasma concentrations by actual sampling times will be provided by analyte and participant (one participant per plot, 6 plots per page). All treatments will be displayed on the same plot. These plots will show time in hours. MD plots will show the complete profile. Individual plots will use the BLQ handling procedure described below for “Pharmacokinetic Parameters”. The Y axis will be allowed to adjust dynamically for each individual plot.

All individual participant plasma concentration data will be listed and included in the summary tables.

16.2.2 Pharmacokinetic Parameters

Plasma PK parameters for LY3526318 and LSN3528305 will be estimated using non-compartmental methods with WinNonlin®.

The plasma PK parameters will be estimated from the individual concentration-time profiles. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after 2 or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

Descriptive statistics (number of participants, arithmetic mean, SD, CV%, median, minimum, and maximum, geometric mean and geometric CV%) will be used to summarize the calculated plasma PK parameters by treatment. For T_{max}, only median, minimum and maximum will be presented.

The points to be included in the λ_z range will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles and the points will be indicated in the plots. At least 3 points will be required to be used. The C_{max} data point will not be included. Parameters based on r^2 adjusted below 0.80 or $\%AUC_{extra}$ above 20% will be flagged but not excluded from descriptive statistics or any statistical analysis.

16.2.2.1 Dose-Proportionality

Dose proportionality may be explored for C_{max}, AUC_{0-t}, and AUC_{0-inf} (for SAD) using the power model as described by Smith et al, 2000. In the power model, the log_e-transformed parameters (Y) are assumed to be linearly related to the log_e-transformed Dose:

$log_e = \beta_0 + \beta_1 * log_e(Dose)$

Results will be presented in a table. The table will show the results of the dose proportionality assessment as shown in Table 2 in Smith et al, 2000. If the 90% confidence Intervals (CIs) for the dose-normalized ratio of PK geometric mean values (over the full range of doses tested) is included in the interval (0.8, 1.25) dose proportionality can be assumed. The maximum fold dose range in which dose proportionality can be concluded will also be reported.

16.2.2.2 Food Effect

For the dose level administered in a fasted and fed state (Part A), an analysis of variance (ANOVA) will be performed on AUC_{0-t}, AUC_{0-inf} and C_{max} using the SAS procedure for mixed effect models (PROC MIXED). The PK parameters will be natural logarithm transformed prior to the analysis. The ANOVA model will include fixed effects for treatment and a random effect for participant. From this model the back-transformed least-squares means (LSMeans) for each treatment and their ratio will be presented. The ratio of least-squares geometric means between the test treatment (fed) to the reference (fasted) and the corresponding 90% CI will be presented.

For T_{max}, a Wilcoxon signed rank test will be performed. The median T_{max} for each treatment and the median of pairwise differences between the treatments (fed-fasted) will be presented along with the 90% CIs, and p-values.

17.0 Safety Analyses

17.1 Safety Variables

The following safety variables will be listed and/or summarized:

- Adverse Events (AEs)
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Heart rate
  - Oral body temperature
  - Body Weight
- ECG
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - QTc (Fridericia) Interval
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis
- Physical Examinations
- Columbia-Suicide Severity Rating Scale (C-SSRS)

17.1.1 Adverse Events

All AE summaries will include only treatment-emergent AEs. Treatment-emergent AEs (TEAE) are those which occur after the first dose of study drug. For the SAD part, TEAEs occurring following dosing in a specific period but before dosing in the next period will be attributed to that specific period.

A breakdown of the number of events, and the number and percentage of participants reporting each TEAE, categorized by system organ class (SOC) and preferred term (PT) coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (version as per the Dictionary Coding Conventions), will be presented by treatment, overall active and overall for each study part, in descending order of total number of events by SOC and PT. One table is presented for all TEAEs and one table is presented for TEAEs considered to be related to the study medication. Participants will only be counted once within each SOC or PT per treatment.

Additionally, a summary table with TEAEs by severity and relationship to study drug will be presented by study part and treatment.

TEAEs of which the relationship to study drug will be classified as 'possibly', ''likely', or 'definitely' will be regarded as related, while TEAEs that are classified as 'none', or 'unlikely' will be regarded as not related in the tables

A listing of AEs leading to study discontinuation will be provided.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed.

The following missing data will be imputed as defined (for calculations only/will not be presented):

- Missing AE start and/or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date will be assumed to be after treatment for the determination of TEAE and on treatment for single treatment studies but will not be attributed to treatment in studies with multiple treatments

For the US Clinical Trials Registry (CTR), a CTRAE summary table and the CTRAESUMM SAS dataset will be provided separately from the TFL created for CSR. The table and corresponding dataset will be created according to the specifications provided by the Sponsor.

17.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious AEs (SAE) will be provided by participant.

17.1.3 Laboratory Data

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

All laboratory data (observed values and for clinical chemistry and hematology derived changes from baseline) will be listed, including laboratory variables not listed in the protocol. A separate listing, including out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry and hematology (observed values and derived changes from baseline) by treatment and scheduled time will be presented.

17.1.4 Vital Signs

All vital signs data (observed values and derived changes from baseline) will be listed by participant for all timepoints.

Descriptive statistics will be provided to summarize vital signs (observed values and derived changes from baseline) by treatment and scheduled time.

17.1.5 Electrocardiograms

The observed measurements for all ECG parameters and any corresponding abnormalities and Investigator's conclusion will be listed by participant for all timepoints. The means of triplicate measurements for continuous parameters and the corresponding changes from baseline of the mean triplicate measurements at each scheduled timepoint will be listed by participant.

Descriptive statistics will be provided to summarize mean ECG parameters (observed values and derived changes from baseline) by treatment and scheduled time.

The relationship between LY3526318 PK and QTcF will be graphically explored. Scatter plots of both absolute values and change from baseline QTcF values will be presented, including a calculated regression line showing the relationship. In the change from baseline plots, predose QTcF values will be omitted. PK concentration values below the LLOQ will be set to LLOQ/2.

17.1.6 Physical Examinations

The physical examination findings (abnormalities) at screening and changes from/new findings during study or at follow-up will be listed.

17.1.7 Weight

The results of the body weight measurements will be listed by participant, visit and timepoint.

17.1.8 C-SSRS

The results of the C-SSRS questionnaire will listed by participant for all timepoints.

18.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

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Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
ADAE	AE analysis dataset
ADEG	ECG analysis dataset
ADLB	Laboratory analysis dataset
ADPC	PK concentrations analysis dataset
ADPP	PK parameters analysis dataset
ADSL	Subject level analysis dataset
ADVS	Vital signs analysis dataset
ADaM	Analysis data model
AE	Adverse event
ANOVA	Analysis of variance
BMI	Body mass index
BQL	Below the quantifiable limit
C-SSRS	Columbia-Suicide Severity Rating Scale
CDISC	Clinical Data Interchange Standard Consortium
CI	Conf idence interval
CRU	Clinical research unit
CSR	Clinical study report
CTR	Clinical Trials Registry
CV	Coef ficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
ICH	International Council for Harmonization
LLOQ	Lower limit of quantification
LSMeans	Least-squares means
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-effect level
PDF	Portable document format
PK	Pharmacokinetic(s)
QA'd	Quality assured
QC'd	Quality controlled
SAD	Single ascending dose

SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SDTM	Study data tabulation model
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, f igures and listings
WHO-DDE	World Health Organization – Drug Dictionary Enhanced
WNL	WinNonlin

A detailed description of the PK parameters can be found in Table 2: Plasma PK Parameters.

Appendix 2: Schedule of Assessments

Schedules of procedures are described in:

- Table 3 Study Schedule Protocol J2D-MC-CVAC Single -Ascending Dose (SAD) – Part A
- Table 4 Scheduled Times for PK Blood Sample and ECG for Periods 1 to 4
- Table 5 Study Schedule Protocol J2D-MC-CVAC Multiple Dose (MD) – Part B
- Table 6 Part B Scheduled Times for PK Blood Samples and Single 12-lead ECGs

Table 3 Study Schedule Protocol J2D-MC-CVAC Single -Ascending Dose (SAD) – Part A

	S	Treatment Period[a]						FU	ED[b]
Visit	**1**	**2**				**3**	**4**	**5**	
Study Day	**-28**	**-1[c]**	**1**	**2**	**3**	**4**	**5**	**10 (±1 day)**	
Admit to CRU[d]		X							
Discharge from CRU					X[e]				
CRU visit	X	X				X[e]	X[e]	X	X
Informed consent	X								
Medical history	X	X							
C-SSRS	X	X						X	X
Height	X								
Weight	X	X						X	X
Physical examination	C	D	D	D	D	D	D	D	D
Urine drug screen	X	X						X	X
Hematology and clinical chemistry	X		P	X			X	X	X
Urinalysis[f]	X	X	P	X			X	X	X
β-hCG pregnancy test	X	X						X	X
HIV, HCV, HBsAg	X								
Con med		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Vital signs	X	X	P, 2, 4, 6 h	X	X	X	X	X	X
Temperature	X	X							
ECG[g]	See Table 4								
Randomization			X						
Study intervention administration[h]			X						
PK blood sample[i]		See Table 4							

Abbreviations: C = compete physical examination; Con med = concomitant medications; COVID-19 = coronavirus disease 2019; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; FU = safety follow-up; HBsAg = hepatitis B surface antigen; β-hCG = beta subunit of human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P = predose assessment; PK = pharmacokinetic; S = Screening; SOP = standard operating procedure.

Note: In the event that assessments are planned for the same time, assessments should be conducted in following order: ECG/vital signs/ PK sample The ECG and vital signs measurement can be obtained at least 30 minutes prior to the PK sample, which is drawn at the nominal time point.

Screening visits will be performed within 28 days before the administration of first dose.

[a] The procedures for Days -1 through 5 will be repeated for up to 4 treatment periods.

[b] Participants who discontinue the study prior to study completion will complete the ED visit procedures.

[c] Day -1 procedures can be performed on a day prior to dosing or pre-dose on day of dosing.

[d] All participants will remain in the CRU until completion of all procedures that occur that day.

[e] After participants have completed the required in-house stay, the remaining activities may be completed in house or ambulatory based upon the discretion of the investigator.

[f] A standard urine dipstick may be used.

[g] See Table 4. Triplicate 12-lead ECGs will be obtained with approximately 1 minute apart following at least 10 minutes in the supine position. Single 12-lead ECGs will be collected at the time points indicated.

[h] The exact time that study intervention is administered will be recorded.

[i] See Table 4.

Note: All local requirements regarding COVID-19 will be followed according to local/site SOP.

Table 4 Scheduled Times[a] for PK Blood Sample and ECG for Periods 1 to 4

Day[a]	Time[b]	ECG (Fasted)	ECG (Fed)	PK Sample Periods 1-4
Da y -28 to -1	Screening	Single ECG		
Da y 1	Predose	ECG[c]	Single ECG	X
	Dose			Dose of LY3526318
	1 h			X
	2 h	ECG[c]		X
	4 h	ECG[c]		X
	6 h	ECG[c]		X
	8 h			X
	12 h			X
Da y 2	24 h	ECG[c]		X
Da y 3	48 h			X
Da y 4	72 h			X
Da y 5	96 h			X
Follow-up visit		Single ECG	Single ECG	X
Early Discontinuation		Single ECG	Single ECG	X

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic.

[a] The procedures for Days -1 through 5 will be repeated for up to 4 treatment periods.

[b] Sampling times are given as targets to be achieved within reasonable limits. The timing of PK sample collections may be adjusted based on clinical needs. The exact sample collection dates and times must berecorded.

[c] Following at least 10 minutes in a supine position, triplicate ECG are collected with approximately 1 minute between measurements.

Table 5 Study Schedule Protocol J2D-MC-CVAC Multiple Dose (MD) – Part B

	S	Treatment Period								FU	ED[a]
Visit	1		2							3	
Study Day	-28	-1[b]	1	2	3	4	5	6	7	8	14	
Admit to CRU[c]		X										
Discharge from CRU										Xd		
CRU visit	X	X									X	X
Informed consent	X											
Medical history	X	X										
C-SSRS	X	X									X	X
Height	X											
Weight	X	X									X	X
Physical examination	C	D	D	D	D	D	D	D	D	D	D	D
Urine drug screen	X	X									X	X
Hematology and clinical chemistry	X		P	P		P	P	X	X	X	X	X
Urinalysis[e]	X	X	P	X		X	X	X	X	X	X	X
β-hCG pregnancy test	X	X									X	X
HIV, HCV, HBsAg	X											
Con med		X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	P and 4 h	X	X	X	X	X	X	X	X	X
Temperature	X	X										
ECG[f]			See Table 6									
Randomization			X									
Study intervention administration[g]			X	X	X	X	X					
PK blood sample[h]			See Table 6									

Abbreviations: Con med = concomitant medications; COVID-19 = coronavirus disease 2019; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; FU = safety follow-up; HBsAg = hepatitis B surf ace antigen; β-hCG = beta subunit of human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P = predose assessment; PK = pharmacokinetic; S = Screening; SOP = standard operating procedure.

[a] Participants who discontinue the study prior to study completion will be expected to complete the ED visit procedures.

[b] Day -1 procedures can be performed on a day prior to dosing or predose on day of dosing.

[c] Participants will be confined to the CRU from Day -1 until all study assessments are completed 72 hours after the last dose

[d] After participants have completed the required in-house stay, the remaining activities may be completed in house or ambulatory based upon the discretion of the investigator.

[e] A standard urine dipstick may be used.

[f] A single 12-lead ECG will be obtained in the supine position after at least 10 minutes rest.

[g] The exact time study intervention is administered will be recorded.

[h] See Table 6 Part B Scheduled Times for PK Blood Samples.

Note: Screening visits will be performed within 28 days before the administration of first dose.

Note: In the event that assessments are planned for the same time, assessments should be conducted in following order: ECG/vital signs/PK sample. The ECG and vital signs measurement can be obtained at least 30 minutes prior to the PK sample, which is drawn at the nominal time point.

Note: All local requirements regarding COVID-19 will be followed according to local/site SOP.

Table 6 Part B Scheduled Times for PK Blood Samples and Single 12-lead ECGs

Day	Time[a]	PK Collections[b]	ECG
Day 1	Predose	X	X
	Dose	Dose of LY3526318	
	1 h	X	
	2 h	X	X
	4 h	X	X
	6 h	X	X
	8 h	X	
	12 h	X	
Day 2	Predose (24 hours after the preceding dose)	X	X
	Dose	Dose of LY3526318	
Day 3	Predose (24 hours after the preceding dose)	X	
	Dose	Dose of LY3526318	
Day 4	Predose (24 hours after the preceding dose)	X	
	Dose	Dose of LY3526318	
Day 5	Predose (24 hours after the preceding dose)	X	X
	Dose	Dose of LY3526318	
	1 h	X	
	2 h	X	X
	4 h	X	X
	6 h	X	X
	8 h	X	
	12 h	X	
Day 6	+24 h (24 hours after the preceding dose)	X	X
Day 7	+ 48 h	X	
Day 8	+72 h	X	
Follow-Up		X	
Early Discontinuation		X	X

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic.

[a] Sampling times are given as targets to be achieved within reasonable limits.

[b] The timing of PK sample collections may be adjusted based on clinical needs. The exact sample collection dates and times must be recorded.

Appendix 3: List of End of Text Outputs

The planned TFLs for the CSR are listed below. The placement and numbering presented is for tracking/development purpose and may deviate from the placement order and numbering listed in the CSR.

This list defines the tables to be produced by programming. The medical writer can decide to insert any of the figures or create more tables in the CSR text independently of this SAP.

List of End of Text Tables, Figures and Listings:		
Output	**Title**	**Population Set used in Tables/Figures***
Section 12.1 – Demographic and Other Baseline Data		
Section 12.1.1 Demographic Data		
Listing 12.1.1.1	Subject Randomization and Treatment Assignment	
Table 12.1.1.2	Summary of Subject Disposition	Saf ety
Listing 12.1.1.3	Subject Disposition	
Table 12.1.1.4	Summary of Demographics	Saf ety
Table 12.1.1.5	Summary of Demographics	PK
Listing 12.1.1.6	Subject Demographics	
Listing 12.1.1.7	Analysis Sets	
Section 12.1.2 Other Baseline Data		
Listing 12.1.2.1	Medical History	
Listing 12.1.2.2	Prior and Concomitant Medications	
Listing 12.1.2.3	Results of Serology Tests	
Listing 12.1.2.4	Results of Pregnancy/FSH Tests	
Listing 12.1.2.5	Results SARS-CoV-2 Tests	
Section 12.2 – Compliance Data		
Listing 12.2.1	Study Dates	
Listing 12.2.2	Study Drug Administration	
Listing 12.2.3	Meals (FE periods only)	
Section 12.3 – Safety Data		
Section 12.3.1 – Adverse Events		
Table 12.3.1.1	Deaths and Other Serious Adverse Events	Saf ety
Listing 12.3.1.2	Adverse Events Leading to Study Discontinuation	
Listing 12.3.1.3	Adverse Events	
Table 12.3.1.4	Summary of All Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment	Saf ety

Table 12.3.1.5	Summary of Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment	Saf ety
Table 12.3.1.6	Summary of Treatment-Emergent Adverse Events by Treatment, Relationship and Severity	Saf ety
Section 12.3.2 – Clinical Laboratory Data		
Listing 12.3.2.1	Clinical Laboratory Results - Clinical Chemistry	
Listing 12.3.2.2	Clinical Laboratory Results - Hematology	
Listing 12.3.2.3	Clinical Laboratory Results - Urinalysis	
Listing 12.3.2.4	Clinical Laboratory Results - Alcohol and Drug Screen	
Listing 12.3.2.5	Clinical Laboratory Results - Comments	
Table 12.3.2.6	Summary of Clinical Laboratory Data - Clinical Chemistry	Saf ety
Table 12.3.2.7	Summary of Clinical Laboratory Data - Hematology	Saf ety
Table 12.3.2.8	Out-of -Range Laboratory Values by Subject	Saf ety
Section 12.3.3 Vital Signs Data		
Listing 12.3.3.1	Vital Signs	
Table 12.3.3.2	Summary of Vital Signs	Saf ety
Section 12.3.4 ECG Data		
Listing 12.3.4.1	12-Lead Electrocardiogram Results – Individual Parameters	
Listing 12.3.4.2	12-Lead Electrocardiogram Results – Investigator's Interpretation and Specification of Abnormalities	
Table 12.3.4.3	Summary of 12-Lead Electrocardiogram	Saf ety
Figure 12.3.4.4	Scatter Plots of QTcF versus Plasma Concentrations of LY3526318 (optional)	
Section 12.3.5 Other Safety Data		
Listing 12.3.5.1	Physical Examination Findings and Changes	
Listing 12.3.5.2	Body Weight	
Listing 12.3.5.3	Columbia-Suicide Severity Rating Scale	
Section 12.4 – Pharmacokinetic Data		
12.4.1 SAD Part		
Listing 12.4.1.1	LY3526318 and LSN3528304 Plasma Concentrations, Sampling Time Deviations and Comments	
Table 12.4.1.2	Individual Values and Descriptive Statistics of LY3526318 Plasma Concentrations by Treatment	PK
Table 12.4.1.3	Individual Values and Descriptive Statistics of LSN3528305 Plasma Concentrations by Treatment	PK
Table 12.4.1.4	Individual Values and Descriptive Statistics of LY3526318 Plasma PK Parameters by Treatment	PK

Table 12.4.1.5	Individual Values and Descriptive Statistics of LSN3528305 Plasma PK Parameters by Treatment	PK
Table 12.4.1.6	Dose Proportionality for LY3526318 and LSN3528305	PK
Table 12.4.1.7	Summary Statistical Analysis of Food Effect	PK
Figure 12.4.1.8	Geometric Mean LY3526318 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	PK
Figure 12.4.1.9	Geometric Mean LSN3528305 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	PK
Figure 12.4.1.10	Geometric Mean LY3526318 Plasma Concentrations versus Time Profiles Food Effect on Linear and Semi-Logarithmic Scale	PK
Figure 12.4.1.11	Geometric Mean LSN3528305 Plasma Concentrations versus Time Profiles Food Effect on Linear and Semi-Logarithmic Scale	PK
Figure 12.4.1.12	Combined Individual LY3526318 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety
Figure 12.4.1.13	Combined Individual LSN3528305 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety
Figure 12.4.1.14	Individual LY3526318 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety
Figure 12.4.1.15	Individual LSN3528305 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety
12.4.2 MD Part		
Listing 12.4.2.1	LY3526318 and LSN3528304 Plasma Concentrations, Sampling Time Deviations and Comments	
Table 12.4.2.2	Individual Values and Descriptive Statistics of LY3526318 Plasma Concentrations by Treatment	PK
Table 12.4.2.3	Individual Values and Descriptive Statistics of LSN3528305 Plasma Concentrations by Treatment	PK
Table 12.4.2.4	Individual Values and Descriptive Statistics of LY3526318 Plasma PK Parameters by Treatment	PK
Table 12.4.2.5	Individual Values and Descriptive Statistics of LSN3528305 Plasma PK Parameters by Treatment	PK
Figure 12.4.2.6	Geometric Mean LY3526318 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale Full profile	PK
Figure 12.4.2.7	Geometric Mean LSN3528305 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale Full profile	PK
Figure 12.4.2.8	Geometric Mean LY3526318 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Overlay Day 1 and Day 5	PK
Figure 12.4.2.9	Geometric Mean LSN3528305 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Overlay Day 1 and Day 5	PK

Figure 12.4.2.10	Combined Individual LY3526318 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety
Figure 12.4.2.11	Combined Individual LSN3528305 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety
Figure 12.4.2.12	Individual LY3526318 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety
Figure 12.4.2.13	Individual LSN3528305 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Saf ety

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.7	Randomization
Appendix 16.1.9.2	Statistical Appendices

Document History

PPD


PPD


PPD