Statistical Analysis Plan J2D-MC-CVAA

A Safety, Tolerability, Pharmacokinetic, and Pilot Food Effect Study of Single- and Multiple-Ascending Doses of LY3526318 in Healthy Participants

NCT03977974

Approval Date: 07-Apr-2020

Statistical Analysis Plan

Sponsor:	Eli Lilly and Company
Protocol No:	J2D-MC-CVAA
Protocol Title:	A Safety, Tolerability, Pharmacokinetic, and Pilot Food Effect Study of Single- and Multiple-Ascending Doses of LY3526318 in Healthy Participants
PRA Project ID:	CHO19219-19219X
Version Date:	07-Apr-2020 (SAP)

1.0 Approvals

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

PPD

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-CVAA.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 16-Dec-2019 (including all amendments up to this protocol date) and the final eCRFs (see Table 1).

Table 1 eCRF versions

Cohort	Date
Cohorts 1, 2, 3, 4 (Period 1), and 4	12-Jul-2019
Cohorts 4 (Period 2) and 6	07-Oct-2019
Cohorts 7, 8, and 9	04-Nov-2019
Cohort 10	22-Jan-2020

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 evaluation of:

- pharmacokinetic (PK) data,
- safety and tolerability data.

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 Section 9.8.2 of 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 2 below.

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary (Part A – SAD)	
To evaluate safety and tolerability of LY3526318 in healthy participants following a single oral dose	• Adverse Events (AEs) • Serious Adverse Events (SAEs)
Primary (Part B – MAD)	
To evaluate safety and tolerability of LY3526318 in healthy participants following multiple once-daily oral doses for 14 days	• AEs • SAEs
Secondary (Part A – SAD)	
To evaluate the plasma pharmacokinetics of LY3526318 in healthy participants following a single oral dose	• AUC • C_{max} • t_{max}
Secondary (Part B – MAD)	
To evaluate the plasma pharmacokinetics of LY3526318 in healthy participants following multiple once-daily oral doses for 14 days	• AUC • C_{max} • t_{max}
Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; MAD = multiple ascending dose; SAD = single ascending dose; SAE = serious adverse events; t_{max} = time of C_{max}	

6.0 Study Design

This is a Phase 1 single-center, randomized, double-blind, placebo-controlled, single ascending dose (SAD, Part A) and multiple ascending dose (MAD, Part B) study of LY3526318 in healthy participants.

Part A - SAD

The single-ascending doses of LY3526318 or placebo will be administered, at planned dose levels of 10, 50, 100, 400, 800, and 1000 mg, in 6 cohorts of 8 participants each, except the 100-mg cohort that will include 12 participants. The dose levels may change subject to available safety and PK data review.

Participants in the first cohort (10 mg, Cohort 1) will not be stratified by sex. A fixed number of females and males will be randomized in Cohorts 2 and 3 and the participants will be stratified to ensure equal distribution between females and males. Cohorts administered above LY3526318 100 mg are anticipated to exceed the approximate 10x margin to the projected no-observed-adverse-event-level (NOAEL)-equivalent exposure for males; for this reason, only female participants will be enrolled at dose levels higher than 100 mg. Randomization to LY3526318 or placebo will be 3:1 within each cohort or stratum, respectively.

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. A sentinel dosing strategy will be utilized for the first dose level (Cohort 1, 10 mg). Two participants will receive a sentinel dose (1 each with LY3526318 and placebo) and the remaining participants will be administered after review of safety data up to 48 hours postdose. Dose escalation from the 10-mg to 50-mg cohort may occur after review of safety data from at least 6 participants in the 10-mg cohort. Dose escalations to subsequent cohorts may occur after review of safety data and available PK data through 48 hours postdose from at least 6 participants in the prior cohort.

The effect of food on LY3526318 PK will be explored in female participants only in Cohort 3 and in Cohort 4. The initial dose will be administered after an approximately 8-hour fast, followed by a washout period of at least 1 week, a second dose will be administered after a standardized high-fat meal.

Except for the food effect assessment cohorts, all other doses are to be administered after an approximately 8-hour fast. Following a review of the 100-mg and/or 400-mg fed and fasted data, subsequent cohorts may be administered with food.

An additional cohort (Cohort 10) will assess the effect of timing of food on LY3526318 PK in 8 female participants. All participants in this cohort will received 100 mg LY3526318 with standardized high fat meal in an open-label, 3-way crossover manner (meal administered prior to dose, at 30 minutes and at 1 hour post dose; Table 2-2). Participants receiving meals post dose administration will receive their dose after an approximately 8-hour fast. Periods will be separated by a washout period of at least 1 week.

Participants will return to the CRU for a final follow-up visit approximately 9 days after study drug administration or after the fed-state dose for female participants in the 100- and 400-mg cohorts.

Part B - MAD

The multiple-ascending doses of LY3526318 or placebo will be administered, at planned dose levels of 100, 400, and 1000 mg, once daily for 14 days in 3 cohorts of 8 female participants each. It is likely that 1 or more dose levels in Part B may exceed the approximate 10x margin to the projected NOAEL-equivalent exposures for males; for this reason, only female participants will be enrolled in Part B. The planned dose levels may be updated following a review of safety and PK data from Part A and they will not exceed those studied in Part A.

The first cohort of Part B will be administered LY3526318 following a review of Part A safety and PK data. Dose escalations to subsequent cohorts may occur after review of safety data and available PK data through 14 days from at least 6 participants in the prior cohort.

Following a screening period of up to 28 days, eligible participants will be confined to the CRU from Day -1, until all study assessments are completed on Day 15. Within each cohort, participants will be randomly assigned to receive LY3526318 or placebo in a 6:2 ratio, except for Cohort 10; where all subjects will receive LY3526318 in all 3 periods in a fixed sequence.

LY3526318 or matching placebo is planned to be administered in an 8-hour fasting state once daily for 14 days. However, following a review of the food effect data from Part A, all doses may be administered with food.

Participants will return to the CRU for a final visit on Day 23.

6.1 Sample Size Considerations

Part A: Approximately 60 participants will be randomized to achieve 8 evaluable participants per cohort (6 LY3526318:2 placebo), except for Cohort 3, which was to include 8 evaluable females and 4 evaluable males (females: 6 LY3526318:2 placebo; males: 3 LY3526318:1 placebo) and Cohort 10 (the 100-mg food assessment cohort) which was to include 8 evaluable females (females: 8 LY3526318:0 placebo, open label).

Part B: Approximately 24 participants will be randomized to achieve 8 evaluable participants per cohort (6 LY3526318:2 placebo).

Additional cohorts of up to 8 participants each may be enrolled in either part of the study. Such additional cohorts may be enrolled in case intermediate or additional dose level(s) need to be studied or additional food effect need to be studied at other than planned dose levels.

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered based on statistical hypothesis testing.

6.2 Randomization

A randomization schedule was generated by the EDS Biostatistics department of PRA for all cohorts except Cohort 10 according to the study specific Randomization Specifications created by then PRA biostatistician and approved by the Sponsor.

Part	Cohort	Period	Planned Treatment[#]	Actual Dose[#]	♀	♂	Stratified by sex
A	1a (sentinel)	1	10 mg LY3526318 or Placebo	10 mg	2		No
	1b	1	10 mg LY3526318 or Placebo	10 mg	6		No
	2	1	50 mg LY3526318 or Placebo	50 mg	4	4	Yes
	3	1	100 mg LY3526318 or Placebo	100 mg	8	4*	Yes
		2	100 mg LY3526318 or Placebo fed	30 mg	8		NA
	4	1	400 mg LY3526318 or Placebo	200 mg	8		NA
		2	400 mg LY3526318 or Placebo fed	200 mg	8		NA
	5	1	800 mg LY3526318 or Placebo	300 mg	8		NA
	6	1	1000 mg LY3526318 or Placebo	30 mg	8		NA
	10 (additional)	1	100 mg LY3526318 Fed standardized high fat meal to start 30 minutes prior to dose administration	100 mg	8		NA
		2	Fasted at least 8 hours predose with a standardized high fat meal administered 30 minutes post dose	100 mg			
		3	Fasted at least 8 hours predose with a standardized high fat meal administered 1 hour post dose	100 mg			
	11 (additional)	1	TBD mg LY3526318 or Placebo	NA	8		NA
B	7	1	100 mg LY3526318 or Placebo QD	30 mg	8		NA
	8	1	400 mg LY3526318 or Placebo QD	60 mg	8		NA
	9	1	Up to 1000 mg LY3526318 or Placebo QD	100 mg	8		NA
	12 (additional)	1	TBD mg LY3526318 or Placebo QD	NA	8		NA
	13 (additional)	1	TBD mg LY3526318 or Placebo QD	NA	8		NA

[#]) Doses may be adjusted based on data obtained in previous study cohorts, see actual dose column for the adjusted doses.

*) As a result of exposures found in the interim PK data after Cohort 2 being higher than expected, it was decided not to dose male subjects with a 100 mg dose in Cohort 3 and therefore the number of subject in this cohort was also 8.

NA=not applicable, TBD=to be determined.

Replacement subjects will receive the same randomization number as the subject to be replaced increased by 1000 and will be administered the same.

In Cohorts 3 and 4 the female subjects will be dosed in a 2nd period in which they were to receive the same treatment under fed conditions. After evaluation of the interim PK results, it was decided to reduce the dose level of Period 2 for Cohort 3 to 30 mg under fed conditions.

An additional cohort (Cohort 10) will assess the effect of food on LY3526318 PK in 8 female participants. All participants in this cohort will receive 100 mg LY3526318 with a standardized high fat meal in an open-label, 3-way one-sequence crossover manner (meal administered prior to dose, at 30 minutes and at 1 hour post dose; Table 2-2). Participants receiving meals post dose administration will receive their dose after an approximately 8-hour fast. Periods will be separated by a washout period of at least 1 week.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

In Section 6.0 Study Design above, wording has been adapted from the protocol to reflect actual execution rather than planned. For instance, actual doses have been added and the fact that it was decided not to dose male subjects with a 100 mg dose in Cohort 3.

7.2 Interim Analysis and Key Results

Interim PK reports will be provided by the PRA EDS biostatistics department after completion of each Cohort, except for Cohort 1 (Part A) and the last Cohort of Part B. These reports will be created from blinded concentrations versus scheduled time data provided by the PRA bioanalytical laboratory.

7.3 Final Analysis

Draft TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized.

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 tables, figures and listings (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 four 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 (min) value,
- median, and
- maximum (max) value.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects 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 treatment (and time point, if applicable). Placebo data will be pooled for Parts A (SAD) and B (MAD). Placebo data from the periods under fed conditions (i.e. Period 2 for Cohorts 3 and 4) will be pooled and reported as separated treatment.

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. Except for 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 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.

9.2.2 Treatment/Subject Grouping

In summary tables, data will be presented by study part and treatment.

Table 3 Part, Cohort and Treatment Labels

Label	Grouping
Study Part	Part A (SAD) Part B (MAD)
Cohorts	Part A: 1-6 and 10 Part B: 7-9
Planned Treatments	Part A (SAD): – Placebo – Placebo fed – 10 mg LY – 50 mg LY – 100 mg LY – 30 mg LY fed – 200 mg LY – 200 mg LY fed – 300 mg LY – 100 mg LY fed (-30 min) – 100 mg LY fed (+30 min) – 100 mg LY fed (+60 min) Part B (MAD): – Placebo QD – 30 mg LY QD – 60 mg LY QD – 100 mg LY QD

LY = LY 3526318; QD = once daily

For subjects for which the actual treatment received does not match the planned treatment, the treatment actually received will be used for the analysis. in any summaries or analysis. In case this leads the number of subjects receiving those actual treatments being less than 2, the data for these subjects will only be listed and not included in any summaries or analyses.

9.2.3 Common Variable Derivations

Table 4 Common Variable Derivations

Variable	Definition/Calculation	Variable Name*
Change from Baseline	Post-dose Observation minus Baseline Observation	CHG
Analysis Study Day	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 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 end-point of this study are AEs and SAEs the analysis datasets considered critical are subject level dataset (ADSL) and the adverse events analysis dataset (ADAE). As these are related to the primary objectives these datasets will be double programmed per the QC Plan. In addition, double programming will be used to check the ADPP dataset.

9.2.5 ADaM Datasets and Metadata

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

Table 5 ADaM datasets

ADaM Dataset Name	Description
ADSL	Subject Level Analysis Dataset
ADAE	Adverse Events Analysis Dataset
ADEG	ECG Analysis Dataset
ADLB	Laboratory Test Results Analysis Dataset
ADPC	Pharmacokinetic Concentrations Analysis Dataset
ADPP	Pharmacokinetic Parameters Analysis Dataset
ADVS	Vital Signs Analysis Dataset

ADaM compliant datasets will be delivered to the sponsor. A define.xml file 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

The layout of Tables, Figures and Listings (TFLs) will be according to the PRA EDS standards and will be provided in in Adobe PDF format. Any in-text tables will be provided as RTF tables and in-text figures will be provided as

Format:

- Page size: LETTER
- Data in listings will be sorted by study part, subject number and time point.
- Data in safety and PK concentration tables will be sorted by study part, treatment and time point.
- Column titles will be in title case letters.
- All tables and listings will be in landscape format.
- The treatment labels used in TFL will be as outlined in Table 3, Section 9.2.2.

Any in-text tables will be provided as RTF tables and in-text figures will be provided as PNG files.

10.0 Analysis Sets

Analyses	Randomized Set	Safety Set	Pharmacokinetic Set
Disposition Summaries	✓		
Safety Assessments		✓	
Baseline Characteristics		✓	
Primary Analysis		✓	
PK Concentrations			✓
PK Parameters			✓

10.1 Randomized Set

The all subjects randomized set will consist of subjects who are assigned a randomization number in the study. This set will be used for disposition summaries.

10.2 Safety Set

The safety set will consist of subjects who receive at least one dose of study drug (LY3526318 or placebo). This set will be used for the safety data summaries, baseline characteristic summaries, and PK concentration summaries.

10.3 Pharmacokinetic Set

All participants administered with LY3526318 who have evaluable plasma and/or urine LY3526318 concentrations will be included in the PK analyses. Pharmacokinetic parameter estimates for LY3526318 will be computed using standard noncompartmental methods of analysis.

11.0 Subject Disposition

All disposition data (collected in the SDTM DS domain) will be listed. All subjects who discontinue from the study will be identified.

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

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 subject.

Subject demographics will be summarized descriptively for all subjects by part and treatment. The summary will include the subjects' age (in years), gender, race, ethnicity, weight (in kg), height (in cm), and body mass index (BMI, in kg/m^2). 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 will be listed.

Non-compliance to in- or exclusion criteria (if any) will be listed.

14.0 Concomitant Medications

Concomitant medications will be listed by subject. 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 WHODrug dictionary (WHODrug Global B3 SEP2019).

15.0 Treatment Compliance and Exposure

All exposure data will be listed by subject.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

16.1.1 Plasma Variables

16.1.1.1 Concentrations

- Plasma concentrations of LY3526318 (in mass/volume units)
- Plasma concentrations of LSN3528305 (in mass/volume units)

16.1.1.2 Parameters

- Plasma PK Parameters for LY3526318 as defined in Table 6.
- Plasma PK Parameters for LSN3528305 as defined in Table 6.

Table 6 Plasma PK Parameters

Parameter* (unit)	Description	SAD	MAD Day 1	MAD Day 14	SAS Programming Notes
C_{max} (ng/mL)	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation	✓	✓	✓	Cmax from WNL
T_{max} (h)	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, in hours (h)	✓	✓	✓	Tmax from WNL
λ_z (/h)	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 three 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 ≤ 0.80 then the parameter is flagged (but not excluded from descriptive statistics)
$t_{1/2}$ (h)	Terminal phase half-life expressed in time units. Percent extrapolation less than or equal to 20% and r^2 greater than 0.80 is required to obtain a reliable $t_{1/2}$	✓	(✓)	(✓)	HL_Lambda_z from WNL If Rsq adjusted ≤ 0.80 then the parameter is flagged (but not excluded from descriptive statistics)
$AUC_{0\text{-last}}$ (ng·h/mL)	Area under the concentration-time curve (time 0 to time of last quantifiable concentration)	✓			AUClast from WNL
$AUC_{0\text{-inf}}$ (ng·h/mL)	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 $AUC_{0\text{-inf}}$, in ng·h/mL	✓			AUCINF_obs from WNL If AUC_%Extrap_obs >20% and Rsq adjusted ≤ 0.80 then parameter is flagged (but not excluded from descriptive statistics)
$AUC_{0\text{-24}}$ (ng·h/mL)	Area under the concentration-time curve (time 0 to 24h), in ng·h/mL	✓	✓		
$AUC_{0\text{-24,SS}}$ (ng·h/mL)	Area under the plasma concentration-time curve over the dosing interval (24h) at steady state, in ng·h/mL			✓	AUCtau from WNL where tau is equal to 24 h, if missing for a subject then AUC at nominal time 24 h from summary file is used for $AUC_{0\text{-tau}}$

Parameter* (unit)	Description	SAD	MAD Day 1	MAD Day 14	SAS Programming Notes
CL/F (L/h)	Apparent oral clearance, calculated as Dose/$AUC_{0\text{-}inf}$ for the SAD regimens or Dose/$AUC_{0\text{-}tau}$ for the MAD regimens on Day 14 For parent compound (LY3526318) only, in L/h	✓		✓	CL_F_obs or CLss_F from WNL respectively. If AUC_%Extrap_obs >20% and Rsq adjusted ≤ 0.80 then parameter is flagged (but not excluded from descriptive statistics)
V_z/F (L)	Apparent volume of distribution calculated as $(CL/F)/\lambda_z$ For parent compound (LY3526318) only, in L	✓		✓	Vz_F_obs from WNL.
AR_{AUC}	Accumulation ratio calculated as: $AR_{AUC} = \frac{AUC_{0-24,SS}}{AUC_{0-24,Day\,1}}$			✓	Calculated in SAS by dividing the AUCtau from WNL on Day 14 by the AUC0-24 on day 1.
LI	Linearity index factor of pharmacokinetics after repeated administration $LI_{AUC} = \frac{AUC_{0-24,SS}}{AUC_{0-inf,Day\,1}}$			✓	Calculated in SAS by dividing the AUCtau from WNL on Day 14 by the AUCINF_obs from WNL on day 1 if feasible (i.e., if AUCINF_obs can be estimated).

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

✓ = Will be calculated. (✓) = Will only be calculated if feasible.

*) In End-of-text TFL, subscript will not be used.

16.1.2 Urine Variables

16.1.2.1 Concentrations

- Urine concentrations of LY3526318 and LSN3528305 measured in the 0-24h collection interval (Part A only) in mass per volume units

16.1.2.2 Amounts Excreted

The Amount of LY3526318 and LSN3528305 excreted (Ae) in urine in the 0-24h collection interval (Part A only) will be calculated as:

$Ae_{0-24} = C \times V$

Where, C is the concentration of LY3526318 or LSN3528305 measured in the 0-24h collection interval and V is the volume of urine collection.

16.1.2.3 Parameters

- PK Parameters for LY3526318 and LSN3528305 as defined in Table 7

Table 7 Urine PK parameters

Parameter	Description	SAS Programming Notes
Ae_{0-24} (mg)	Amount of drug excreted unchanged into urine in the 0-24h collection interval in mg, calculated as $Ae_{0-24} = C \times V$ where, C is the concentration of LY3526318 measured in the 0-24h collection interval and V is the volume of urine collection	Calculated by multiplying the urine concentration measured in the 0-24h urine collection interval sample in ng/mL times the volume of the sample in mL
Fe_{0-24} (%)	Fraction (%) of the administered dose excreted unchanged into urine, calculated as $Fe_{0-24} = \frac{Ae_{0-24}}{Dose} \times 100\%$	Calculated by dividing the amount excreted by the (planned) dose of LY3526318 administered.
CL_R (L/h)	Renal clearance calculated as $CL_R = \frac{Ae_{0-24}}{AUC_{0-24}}$ Where Ae_{0-24} is the amount excreted defined above and AUC_{0-24} is the area under the plasma concentration-time curve for time 0 to 24h as defined in Table 6 above.	Calculated by the dividing the amount excreted by the area under the plasma concentration-time curve for time 0 to 24h as obtained from WNL

16.2 Pharmacokinetic Summaries

16.2.1 Pharmacokinetic Concentrations

Plasma concentrations for LY3526318 below the quantifiable limit (BQL) will be set to ½ lower limit of quantification (LLOQ) in the computation of descriptive statistics of concentration values. Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, 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 the subjects 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. All other statistics except the maximum will be missing.

Linear and semi-logarithmic plots of the geometric mean plasma concentration versus scheduled sampling time will presented by part showing all fasted treatments in a single figure.

Separate geometric mean linear and semi-logarithmic plots will show the effect of food given at the same dose (fed versus fasted) for the 30 mg and 200 mg cohorts, that is: Cohort 3 Period 2 and Cohort 6 Period 1 for 30 mg and Cohort 4 Periods 1 and 2 for 200 mg. Also separate geometric mean linear and semi-logarithmic plots will show the effect of food and the timing of food given at the 100 mg dose level (predose, 30 min postdose and 1 hour postpose and fasted) from Cohort 10 Periods 1-3 and Cohort 3 Period 1, respectively. 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 subjects have values BQL.

For the multiple dose part, geometric mean profiles will presented for all treatments in a single plot with a Day 1 and Day 14 profiles superimposed. In addition, linear geometric mean through plasma concentrations versus scheduled sampling time will be presented. These trough plots will include all trough concentrations from time zero on Day 1 up to 24 hours after dosing on Day 14.

Linear and semi-logarithmic plots of the of combined individual plasma concentration versus actual sampling times will be provided by treatment, showing all subjects that received active treatment in one plot for each dose level. These plots will show time in hours and will use the BQL handling procedure described below for “Pharmacokinetic Parameters”. For the MAD Part, these plots will be presented for Day 1 and Day 14 separately.

Linear and semi-logarithmic plots of the individual concentration by actual sampling time will be provided by subject (one subject per plot, 6 plots per page). These plots will show time in hours and will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

Individual plasma concentration data will be presented together with descriptive statistics by treatment.

Individual urine concentrations will be listed together with the sample weight/volume and the derived excretion parameters.

16.2.2 Pharmacokinetic Parameters

Plasma PK parameters for LY3526318 will be estimated using non-compartmental methods with WNL.

The plasma PK parameters will be estimated from individual concentration-time data. 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 two 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.

The points to be included in the λz range will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used. The C_{max} data point will not be included.

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

Urine PK parameters will be derived in SAS. Descriptive statistics (number of subjects, arithmetic mean, geometric mean, standard deviation, arithmetic and geometric CV median, minimum, and maximum) will be used to summarize the calculated urine PK parameters by treatment.

16.2.2.1 Dose-Proportionality

Dose proportionality will be explored for C_{max} and $AUC_{0\text{-}inf}$ (for SAD) or $AUC_{0\text{-}24,SS}$ (for MAD) using the power model as described by Smith et al, 2000. If $AUC_{0\text{-}inf}$ cannot be calculated in many profiles rendering the relationship suspect, $AUC_{0\text{-}24}$ will be used instead. In the power model, the $\log_e$-transformed parameters (Y) are assumed to be linearly related to the $\log_e$-transformed Dose:

$$\log_e Y = \beta_0 + \beta_1 \cdot \log_e(Dose)$$

Results will be presented both in a table and graphically. 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.

In the dose proportionality figures, the individual C_{max} and AUC values will be plotted against the dose and the power model fit together with the corresponding 90% prediction limits and an additional line showing the best straight line through the origin (i.e., $Y = \beta \cdot Dose$) will be presented (see Fig 1 in Smith et al, 2000). The equations (showing final parameter estimates) of the best fit power and linear models will be displayed.

16.2.2.2 Food Effect

The effect of food and the timing of food will be graphically presented using box-plots showing $AUC_{0\text{-}24}$, C_{max} versus treatment. This will be done in separate plots for the following comparisons:

- 100 mg LY fasted, 100 mg LY QD (Day only), 100 mg LY fed (-30 min), 100 mg LY fed (+30 min), and 100 mg LY fed (+60 min)
- 30 mg LY fasted (Cohort 6 Period 1) and 30 mg LY fed (Cohort 3 Period 2)
- 200 mg LY fasted 200 mg LY fed (Cohort 4 Periods 1 and 2)

In addition, for the 200 mg dose level (i.e. Cohort 4 Periods 1 and 2), an analysis of variance (ANOVA) will be performed on $AUC_{0\text{-}24}$ and C_{max} using the SAS PROC MIXED to estimate the geometric mean ratio and corresponding 90% CIs. Dose normalized PK parameters will be natural logarithm transformed prior to the analysis. The model will include fixed effects for food consumption status (fasted or fed) and a random effect for subject. From this model the back-transformed least-squares means (LSMeans) for each treatment and their ratio will be estimated. The ratio of least-squares geometric means between fed and fasted condition and the corresponding 90% CI will be presented.

16.2.3 Pharmacokinetic Amounts Excreted

The volumes of the urine 0-24h collection intervals and the concentrations measured in these intervals as well as the start and end times of the urine collection and the derived amounts excreted in each interval will be listed by subject.

Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be used to summarize the amounts of LY3526318 excreted in urine.

17.0 Pharmacodynamic and Biomarker Analysis

Not applicable.

18.0 Safety Analyses

18.1 Safety Variables

The following safety variables will be summarized:

- AEs
- Vital Signs (measurement after 5 minutes of rest in supine position)
  - Supine Blood Pressure
    - Systolic Blood Pressure (SBP) [mmHg]
    - Diastolic Blood Pressure (DBP) [mmHg]
  - Pulse rate [bpm]
  - Oral body temperature [C]
  - Body Weight [kg]
- Electrocardiogram (ECG) parameters (measurement after 5 minutes of rest in supine position)
  - Heart Rate [bpm]
  - PR-Interval [ms]
  - QRS-Duration [ms]
  - QT-Interval [ms]
  - QTc Fridericia [ms]
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis
- Columbia-Suicide Severity Rating Scale (C-SSRS)

18.1.1 Adverse Events

Treatment-emergent adverse events (TEAE) are those which occur after the first dose of study drug.

All AEs (including non-treatment-emergent events) will be listed, including the AE description (verbatim term), Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT), start date and time, end date and time, severity, relation to study drug, seriousness, action taken, and outcome.

All AE summaries will include only TEAE. All TEAEs occurring following dosing will be attributed to the treatment that was received.

A breakdown of the number of TEAEs, and the number and percentage of subjects reporting each TEAE, categorized by system organ class and preferred term coded according to MedDRA (Version 22.1), will be presented by treatment and overall for each study part. One table is presented for all TEAEs and one table is presented for TEAEs considered to be related to the study medication. Subjects 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.

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
- Missing AE start date will be assumed to be after treatment for the determination of TEAE and on treatment

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.

18.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events (SAE) will be provided by subject.

18.1.3 Laboratory Data

Clinical laboratory data will be presented using standard units from the SDTM Controlled Terminology.

All laboratory data will be listed by subject, 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, hematology and coagulation (absolute observed and derived changes from baseline) by treatment and scheduled time will be presented.

18.1.4 Vital Signs

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

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

18.1.5 Electrocardiograms

The observed measurements and derived changes from baseline for all ECG parameters and any corresponding abnormalities will be listed by subject for all timepoints.

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

Scatter plots of both absolute and changes from baseline QTcF values versus time-matched (predose and 2, 4, and 8 hours postdose) will be presented. In the plots for change from baseline QTcF values predose values will be omitted. Any concentration values below the <LLOQ will assumed to be LLoQ/2.

18.1.6 Physical Examinations

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

18.1.7 Weight

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

18.1.8 C-SSRS

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

19.0 References

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

Clinical Study Protocol. A Safety, Tolerability, Pharmacokinetic, and Pilot Food Effect Study of Single- and Multiple-Ascending Doses of LY3526318 in Healthy Participants. Approved, 09 May 2019.

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000 Oct; 17(10):1278-83.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADaM	Analysis data model
ANOVA	Analysis of variance
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CRU	Clinical research unit
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale ()
CTR	Clinical Trials Registry
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-event level
PK	Pharmacokinetic
PT	Preferred term
QA'd	Quality assured
QC'd	Quality controlled
SAD	Single ascending dose
SAP	Statistical analysis plan
SAE	Serious adverse event
SDTM	Study data tabulation model
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WNL	WinNonlin

Appendix 2: Schedule of Assessments

Study Schedule Protocol J2D-MC-CVAA: Part A Cohorts 1-6 (SAD)

	S	Treatment/ In CRU				Posttreatment	ED[a]
Study Day	≤28	-1	1	2	3	10	
Visit Window (days)						±2	
Visits	1[b]	2[c]				3	
CRU admission		X					
CRU discharge					X		
Participant information (including I/E criteria)	X	X					
Informed consent	X						
Medical history	X						
Height	X						
Weight	X		X			X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	C	C
Urine drug screen and ethanol test	X	X					
Vital signs including temperature	X	X	X (predose, 2 h, 4 h, 8 h)	X	X	X	X
Hematology and clinical chemistry	X	X		X[d]	X[d]	X	X
Urinalysis[e]	X	X					
Pregnancy test (serum beta-hCG)[f]	X	X				X	X
HIV, HCV, HBsAg	X						
ECG[g]	X		X (predose, 2 h, 4 h, 8 h)			X	X
C-SSRS	X	X				X	X
Randomization			X				
Study drug administration[h]			X				
PK blood sample[i]			X	X	X		X
PK 24-hour urine collection[j]			← X →				
Adverse event	← X →						
Concomitant medications	← X →						

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hour; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; PK = pharmacokinetics; S = screening; SAD = single-ascending dose.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of the first dose being administered.

[c] All participants will remain in the CRU until completion of Day 3 procedures.

[d] Hematology and clinical chemistry sample to be taken in the morning.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest.

[h] All doses are planned to be administered in a fasting state (at least 8 hours predose and 4 hours postdose), with the exception of the 100- and 400-mg cohorts. In both cohorts, the initial dose will be administered to participants in the fasted state (at least 8 hours predose and 4 hours postdose), followed by a washout period of at least 1 week and a second dose administration after a standardized high-fat meal. Only female participants will undergo fed dose administration in the 100-mg cohort. Following a review of the 100- and 400-mg fed and fasted data, subsequent cohorts may be administered with food. The exact time study drug is administered will be recorded.

[i] On Day 1, PK samples will be collected at time zero (predose) and at approximately 1, 2, 4, 6, 8, and 12 hours after dosing. One PK sample will be taken at 24 and 48 hours postdose (Days 2 and 3), and if applicable, at the ED Visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time collection intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. The ±5% time window also applies to the start and end times of urine collection intervals. Post-assay remainder PK plasma samples may be stored for metabolite identification.

[j] Urine collection interval is 0 to 24 hours postdose. The total urine volume of the 0- to 24-hour collection will be recorded.

Study Schedule Protocol J2D-MC-CVAA: Part A Cohort 10 (3-Period Food Effect Cohort)

	S	Treatment/ In CRU					Posttreatment	ED[a]
Study Day (visit window)	**≤28**	**-1**	**1**	**2**	**3**	**4**	**10 (± 2)**	
Period		**1-3**					**3**	**1-3**
Visits	**1[b]**	**2[c]**					**3**	
CRU admission		X						
CRU discharge						X		
Participant information (including I/E criteria)	X	X						
Informed consent	X							
Medical history	X							
Height	X							
Weight	X		X				X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	C	C
Urine drug screen and ethanol test	X	X						
Vital signs including temperature	X	X	X (predose, 2 h, 4 h, 8 h)	X	X		X	X
Hematology and clinical chemistry	X	X		X[d]	X[d]		X	X
Urinalysis[e]	X	X						
Pregnancy test (serum beta-hCG)[f]	X	X					X	X
HIV, HCV, HBsAg	X							
ECG[g]	X		X (predose, 2 h, 4 h, 8 h)				X	X
C-SSRS	X	X					X	X
Randomization			X[h]					
Study drug administration[i]			X					
PK blood sample[j]			X	X	X	X		X
PK 24-hour urine collection[k]			← X →					
Adverse event	← X →							
Concomitant medications	← X →							

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hour; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; PK = pharmacokinetics; S = screening; SAD = single-ascending dose.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of the first dose being administered.

[c] All participants will remain in the CRU until completion of Day 4 procedures.

[d] Hematology and clinical chemistry sample to be taken in the morning.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest.

[h] randomization will occur during first period only.

[i] Doses are planned to be administered as follows in each period:

- Period 1-Fed standardized high fat meal to start 30 minutes prior to dose administration
- Period 2-Fasted at least 8-hours predose with a standardized high fat meal administered 30 minutes post dose
- Period 3-Fasted at least 8-hours predose with a standardized high fat meal administered 1 hour post dose

Periods will be separated by a washout of at least 1 week. The meals administered in all treatment periods should be consumed within 30 minutes. The exact time study drug is administered will be recorded.

[j] In each treatment period, on Day 1, PK samples will be collected at time zero (predose) and at approximately 1, 2, 4, 6, 8, and 12 hours after dosing. One PK sample will be taken at 24, 48, and 72 hours postdose (Days 2, 3, and 4), and if applicable, at the ED Visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time collection intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. The ±5% time window also applies to the start and end times of urine collection intervals. Post-assay remainder PK plasma samples may be stored for metabolite identification.

[k] Urine collection interval is 0 to 24 hours postdose. The total urine volume of the 0- to 24-hour collection will be recorded.

Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 7

	S	Treatment/In CRU							Post treatment	ED[a]
Study Day	≤28	-1	1	2	3	5	8	14	15	23	
Visit Window (days)										±2	
Visits	1[b]	2								3	
CRU admission		X									
CRU discharge									X		
Participant information (including I/E criteria)	X	X									
Informed consent	X										
Medical history	X										
Height	X										
Weight	X		X							X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D		C	C
Urine drug screen and ethanol test	X	X									
Vital signs including temperature[c]	X	X	X	X	X	X	X	X		X	X
Hematology and clinical chemistry[d]	X	X		X			X	X		X	X
Urinalysis[e]	X	X									
Pregnancy test (serum beta-hCG)[f]	X	X								X	X
HIV, HCV, HBsAg	X										
ECG[g]	X		X					X		X	X
C-SSRS	X	X							X	X	X
Randomization			X								
Study drug administration[h]			← X →								
PK blood sample[i]			X	X	X	X	X	X	X		X
Adverse event	← X →										
Concomitant medications	← X →										

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Days 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. On Day 2 (at predose) and on Day 15 (prior to discharge), 1 PK sample will be taken at 24 hours postdose. Predose PK samples will also be obtained on Days 3, 5, and 8. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 8

	S	Treatment/In CRU										Post treatment	ED[a]
Study Day	≤28	-1	1	2	3	5	8	14	15	16	17	18	23	
Visit Window (days)													±2	
Visits	1[b]	2											3	
CRU admission		X												
CRU discharge												X		
Participant information (including I/E criteria)	X	X												
Informed consent	X													
Medical history	X													
Height	X													
Weight	X		X										X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D	D	D	D		C	C
Urine drug screen and ethanol test	X	X												
Vital signs including temperature[c]	X	X	X	X	X	X	X	X					X	X
Hematology and clinical chemistry[d]	X	X		X			X	X					X	X
Urinalysis[e]	X	X												
Pregnancy test (serum beta-hCG)[f]	X	X											X	X
HIV, HCV, HBsAg	X													
ECG[g]	X		X					X					X	X
C-SSRS	X	X										X	X	X
Randomization			X											
Study drug administration[h]			← X →											
PK blood sample[i]			X	X	X	X	X	X	X	X	X	X		X
Adverse event	← X →													
Concomitant medications	← X →													

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Day 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. Predose PK samples will also be obtained on Days 2, 3, 5, and 8. One PK sample will be taken at approximately 24, 48, 72, and 96 hours post Day 14 dose on Days 15, 16, 17, and 18, respectively. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 9

	S	Treatment/In CRU												Post treatment	ED[a]
Study Day	≤28	-1	1	2	3	5	8	14	15	16	17	18	19	23	
Visit Window (days)														±2	
Visits	1[b]	2												3	
CRU admission		X													
CRU discharge													X		
Participant information (including I/E criteria)	X	X													
Informed consent	X														
Medical history	X														
Height	X														
Weight	X		X											X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D	D	D	D	D	D	C	C
Urine drug screen and ethanol test	X	X													
Vital signs including temperature[c]	X	X	X	X	X	X	X	X						X	X
Hematology and clinical chemistry[d]	X	X		X			X	X						X	X
Urinalysis[e]	X	X													
Pregnancy test (serum beta-hCG)[f]	X	X												X	X
HIV, HCV, HBsAg	X														
ECG[g]	X		X					X						X	X
C-SSRS	X	X											X	X	X
Randomization			X												
Study drug administration[h]			← X →												
PK blood sample[i]			X	X	X	X	X	X	X	X	X		X		X
Adverse event		← X →													
Concomitant medications		← X →													

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Day 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. Predose PK samples will also be obtained on Days 2, 3, 5, and 8. One PK sample will be taken at approximately 24, 48, 72, and 120 hours post Day 14 dose on Days 15, 16, 17, and 19, respectively. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Appendix 3: List Tables, Figures and Listings Outputs

Table 8 In-Text Tables and Figures

Output	Title	Reference
Section 11 Safety		
Table 11.1	Summary of Demographics (SAD Part)	Table 14.1.2.1
Table 11.2	Summary of Demographics (MAD Part)	Table 14.1.2.1
Table 11.3	Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (SAD Part)	Table 14.3.1.2
Table 11.4	Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (MAD Part)	Table 14.3.1.2
Section 12 Pharmacokinetics		
Table 12.1	Summary of LY3526318 single dose PK parameters (See Appendix 4: Example Tables)	Table 14.2.1.9
Table 12.2	Summary of LSN3528305 single dose PK parameters (See Appendix 4: Example Tables)	Table 14.2.1.10
Table 12.3	Summary of LY3526318 multiple dose PK parameters (See Appendix 4: Example Tables)	Table 14.2.1.9
Table 12.4	Summary of LSN3528305 multiple dose PK parameters (See Appendix 4: Example Tables)	Table 14.2.2.10
Figure 12.5	Geometric Mean LY3526318 Single Dose Plasma Concentrations Versus Time by Treatment under Fasted Conditions (Linear Scale and Semi-Logarithmic Scale)	Figure 14.2.1.3
Figure 12.6	Geometric Mean LSN3528305 Single Dose Plasma Concentrations Versus Time by Treatment under Fasted Conditions (Linear Scale and Semi-Logarithmic Scale)	Figure 14.2.1.4
Figure 12.7	Geometric Mean LY3526318 Single Dose Plasma Concentrations Versus Time by Treatment under Fed Conditions (Linear Scale and Semi-Logarithmic Scale)	Figure 14.2.1.7
Figure 12.8	Geometric Mean LSN3528305 Single Dose Plasma Concentrations Versus Time by Treatment under Fed Conditions (Linear Scale and Semi-Logarithmic Scale)	Figure 14.2.1.7
Figure 12.9	Geometric Mean LY3526318 Multiple Dose Plasma Concentrations Versus Time by Day and Treatment (Linear Scale and Semi-Logarithmic Scale)	Figure 14.2.2.3
Figure 12.10	Geometric Mean LSN3528305 Multiple Dose Plasma Concentrations Versus Time by Day and Treatment (Linear Scale and Semi-Logarithmic Scale)	Figure 14.2.2.4

Table 9 List of End of Text Tables and Figures

Output	Title	Population Set
Section 14.1 Disposition and Demographic Data		
Table 14.1.1	Summary of Subject Disposition	SAF
Table 14.1.2.1	Summary of Demographics	SAF
Table 14.1.2.2	Summary of Demographics	PKAS
Table 14.1.3	Extent of Exposure	SAF
Section 14.2 Pharmacokinetic Data		
Section 14.2.1 SAD Part		
Table 14.2.1.1	Individual Values and Descriptive Statistics of LY3526318 Plasma Concentrations by Treatment	PK
Table 14.2.1.2	Individual Values and Descriptive Statistics of LSN3528305 Plasma Concentrations by Treatment	PK
Figure 14.2.1.3	Geometric Mean LY3526318 Plasma Concentrations Versus Time by Treatment under Fasted Conditions (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.1.4	Geometric Mean LSN3528305 Plasma Concentrations Versus Time by Treatment under Fasted Conditions (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.1.5	Geometric Mean LY3526318 Plasma Concentrations Versus Time by Treatment for 30 and 200 mg Single Doses (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.1.6	Geometric Mean LSN3528305 Plasma Concentrations Versus Time by Treatment for 30 and 200 mg Single Doses (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.1.7	Geometric Mean LY3526318 Plasma Concentrations Versus Time by Treatment for 100 mg Single Doses (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.1.8	Geometric Mean LSN3528305 Plasma Concentrations Versus Time by Treatment for 100 mg Single Doses (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.1.9	Combined Individual LY3526318 Plasma Concentrations versus Time by Treatment (Linear Scale and Semi-Logarithmic Scale)	SAF
Figure 14.2.1.10	Combined Individual LSN3528305 Plasma Concentrations versus Time by Treatment (Linear Scale and Semi-Logarithmic Scale)	SAF
Figure 14.2.1.11	Individual LY3526318 Plasma Concentrations versus Time by Subject (Linear Scale and Semi-Logarithmic Scale)	SAF
Figure 14.2.1.12	Individual LSN3528305 Plasma Concentrations versus Time by Subject (Linear Scale and Semi-Logarithmic Scale)	SAF
Table 14.2.1.9	Individual Values and Descriptive Statistics of LY3526318 PK Parameters by Treatment	PK

Table 14.2.1.10	Individual Values and Descriptive Statistics of LSN3528305 PK Parameters by Treatment	PK
Table 14.2.1.11	Exploratory Statistical Analysis of Dose Proportionality	PK
Figure 14.2.1.12	Boxplots of PK Parameters Versus Treatment for Comparison of Food and Timing of Food Effect	PK
Section 14.2.2 MAD Part		
Table 14.2.2.1	Individual Values and Descriptive Statistics of LY3526318 Plasma Concentrations by Treatment	PK
Table 14.2.2.2	Individual Values and Descriptive Statistics of LSN3528305 Plasma Concentrations by Treatment	PK
Figure 14.2.2.3	Geometric Mean LY3526318 Plasma Concentrations Versus Time by Day and Treatment (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.2.4	Geometric Mean LSN3528305 Plasma Concentrations Versus Time by Day and Treatment (Linear Scale and Semi-Logarithmic Scale)	PK
Figure 14.2.2.5	Geometric Mean LY3526318 Trough Plasma Concentrations Versus Time by Treatment (Linear Scale Scale)	PK
Figure 14.2.2.6	Combined Individual LY3526318 Plasma Concentrations versus Time by Treatment and Day (Linear Scale and Semi-Logarithmic Scale)	SAF
Figure 14.2.2.7	Combined Individual LSN3528305 Plasma Concentrations versus Time by Treatment and Day (Linear Scale and Semi-Logarithmic Scale)	SAF
Figure 14.2.2.8	Individual LY3526318 Plasma Concentrations versus Time by Subject (Linear Scale and Semi-Logarithmic Scale)	SAF
Figure 14.2.2.9	Individual LSN3528305 Plasma Concentrations versus Time by Subject (Linear Scale and Semi-Logarithmic Scale)	SAF
Table 14.2.2.10	Individual Values and Descriptive Statistics of LY3526318 PK Parameters by Treatment	PK
Table 14.2.2.11	Individual Values and Descriptive Statistics of LSN3528305 PK Parameters by Treatment	PK
Table 14.2.2.12	Exploratory Statistical Analysis of Dose Proportionality	PK
Section 14.3 Safety Data		
Section 14.3.1 Adverse Events		
Table 14.3.1.1	Summary of All Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF
Table 14.3.1.2	Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF
Table 14.3.1.3	Summary of Treatment-Emergent Adverse Event by Treatment, Relationship and Severity	SAF
Section 14.3.2 Listing Deaths and Other Serious Adverse Events (If applicable)		

Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	SAF
Section 14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events (Not Applicable)		
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR	
Section 14.3.4 Clinical Laboratory Data		
Table 14.3.4.1	Summary of Clinical Laboratory Data - Clinical Chemistry	SAF
Table 14.3.4.2	Summary of Clinical Laboratory Data - Hematology	SAF
Table 14.3.4.3	Listing of Abnormal Laboratory Values	SAF
Section 14.3.5 Other Safety Parameters		
Table 14.3.5.1	Summary of Vital Signs	SAF
Table 14.3.5.2	Summary of 12-Lead Electrocardiogram	SAF
Figure 14.3.5.3	Scatter Plots of QTcF Versus Plasma Concentrations of LY3526318	SAF

Table 10 List of Subject Data Listings

Output	Title
Section 16.2.1 Disposition	
Listing 16.2.1.1	Subject Disposition
Section 16.2.2 Protocol Deviations	
Listing 16.2.2.1	Not part of TFL – Reserved for protocol deviations in CSR
Section 16.2.3 Excluded Subjects	
Listing 16.2.3	Analysis Sets
Section 16.2.4 Demographics and Baseline Characteristics	
Listing 16.2.4.1	Subject Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Prior and Concomitant Medications
Listing 16.2.4.4	Result of Serology Tests
Listing 16.2.4.5	Result of Pregnancy Tests
Section 16.2.5 Compliance	
Listing 16.2.5.1	Study Dates
Listing 16.2.5.2	Study Drug Administration
Section 16.2.6 Response Data	
Listing 16.2.6.1	LY3526318 Plasma Sampling Time Deviations and Comments
Listing 16.2.6.2	LY3526318 Urine Collection Results
Section 16.2.7 Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Withdrawal
Section 16.2.8 Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry
Listing 16.2.8.2	Clinical Laboratory Results – Hematology
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.4	Clinical Laboratory Results – Alcohol and Drug Screen Test Results
Listing 16.2.8.5	Clinical Laboratory Results – Comments
Section 16.2.9 Other Safety Data	
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.2	12-Lead Electrocardiogram Results – Individual Parameters
Listing 16.2.9.3	12-Lead Electrocardiogram Results – Investigator's Interpretation and Specification of Abnormalities

Appendix 4: Example Tables

Example for Table 12.1: Summary Statistics of Plasma <Analyte> Pharmacokinetic Parameters Following Single Oral LY3526318 Doses in Healthy Subjects, by Treatment and Day (Part A, SAD)

	LY Treatment (fasted)						LY Treatment (fed)				
Dose	**10 mg**	**30 mg**	**50 mg**	**100 mg**	**200 mg**	**300 mg**	**30 mg**	**100 mg (-30 min)**	**100 mg (+30 min)**	**100 mg (+60 min)**	**200 mg**
N	X	X	X	X	X	X	X	X	X	X	X
Plasma Pharmacokinetic Parameters											
AUC_{0-24} (ng•hr/mL)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
AUC_{0-inf_pred} (ng•hr/mL)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
C_{max} (ng/mL)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
t_{max} (hr)*	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
$t_{1/2}$ (hr)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
Urine Pharmacokinetic Parameters											
Ae_{0-24} (mg)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
Fe_{0-24}	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
CL_R (L/hr)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)

Programming notes: Table will created for LY3526318 and LSN3528305

Example for Table 12.2: Summary Statistics of Plasma <Analyte> Pharmacokinetic Parameters Following Multiple Oral LY3526318 Doses in Healthy Subjects, by Treatment and Day (Part B, MAD)

	LY Treatment (fasted)					
Pharmacokinetic Parameters	**30 mg QD**	**60 mg QD**	**100 QD**	**30 mg QD**	**60 mg QD**	**100 mg QD**
Day	**Day 1**			**Day 14**		
N	**X**	**X**	**X**	**X**	**X**	**X**
$AUC_{0\text{-}24}$ (ng•hr/mL)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
$AUC_{0\text{-}inf\_pred}$ (ng•hr/mL)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
C_{max} (ng/mL)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
t_{max} (hr)*	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
$t_{1/2}$ (hr)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)	XXXX (XX.X)
Ra	N/A	N/A	N/A	XX	XX	XX

Abbreviations: $AUC_{0\text{-}24}$ = area under the drug concentration versus time curve from time 0 to the 24 hour measured concentration; $AUC_{0\text{-}inf\_pred}$ = area under the predicted drug concentration versus time curve from time 0 extrapolated to infinity; C_{max} = maximum observed drug concentration; t_{max} = time of maximum observed drug concentration; Ra = accumulation rate based on $AUC_{0\text{-}24}$; $t_{1/2}$ = apparent plasma first-order terminal elimination half-life
N/A - Not applicable
Data shown as geometric mean (CV%) unless otherwise indicated
* = t_{max} is presented as Median (Minimum, Maximum)
Source: Tables XXXX through XXXX

Programming notes: Table will created for LY3526318 and LSN3528305

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
16-Aug-2019	PPD	Created from template EDSREP 009 T 01 G
30-Jan-2020		Updated after protocol amendments and discussion with Sponsor
06-Mar-2020		Updated due to Sponsor comments
26-Mar-2020		Updated due to Sponsor comments