Statistical Analysis Plan J2D-MC-CVAB

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Oral Single-Doses of LY3526318 on Cinnamaldehyde-Induced Dermal Blood Flow in Healthy Females

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Statistical Analysis Plan

Sponsor:	Eli Lilly and Company
Protocol No:	J2D-MC-CVAB(a)
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Oral Single-Doses of LY3526318 on Cinnamaldehyde-Induced Dermal Blood Flow in Healthy Females
PRA Project ID:	CHO19420-19420X
Version Date:	11-Feb-2020

1.0 Approvals

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

Name of Sponsor Representative / Title:	PPD Lead Statistician Chorus
Signature of Sponsor Representative / Date:	PPD
Name of Author / Title:	PPD Pharmaceutical Research Associates Group B.V., a PRA Health Sciences company
Signature of Author / Date:	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-CVAB(a).

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 15-Nov-2019 (including all amendments up to this protocol date) and the final eCRF(s) dated 03-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 the pharmacokinetic (PK), pharmacodynamic (PD), 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

5.1 Primary

To assess target engagement of TRPA1 after a single dose of LY3526318.

5.1.1 Primary Endpoint

Decrease in cinnamaldehyde (CA)-induced dermal blood flow (DBF) relative to placebo measured by laser Doppler Imaging (LDI) at 3 hours post-dose.

5.2 Secondary

- To evaluate the safety and tolerability in healthy females following single oral doses of LY3526318.
- To assess target engagement of TRPA1 after a single dose of LY3526318 using Laser Speckle Contrast Imaging (LSCI), an alternate imaging method.
- To assess the pharmacokinetics of LY3526318 following single oral doses of LY3526318.

5.2.1 Secondary Endpoints

- Treatment-emergent (TE) adverse events (AE), serious AEs.
- Decrease in CA-induced DBF relative to placebo measured by LSCI at 3 hours post-dose.
- Summary of LY3526318 plasma concentrations by dose and time point.

5.3 Exploratory

- To assess target engagement of TRPA1 after a single dose of LY3526318.
- To explore the relationship between LY3526318 plasma concentration and DBF in healthy females following a single oral LY3526318 dose.

5.3.1 Exploratory Endpoints

- Decrease in CA-induced DBF relative to placebo measured by LDI at 24 hours post-dose.
- Decrease in CA-induced DBF relative to placebo measured by LSCI at 24 hours post-dose.
- LY3526318 plasma concentrations.
- DBF.

5.4 Study Hypothesis

The null hypothesis H_0 is that there is no decrease in CA-induced DBF relative to placebo measured by laser Doppler Imaging (LDI) at 3 hours post-dose at an α level of (0.05/3), one-sided. Bonferroni adjustment is used to account for the three comparisons (dose levels) versus placebo.

If the null hypothesis is rejected for any of the dose levels, the alternative hypothesis, i.e. there is a decrease for this dose level, will be accepted.

6.0 Study Design

This is a Phase 1 randomized, double-blind, placebo-controlled, 4-way crossover study of LY3526318 in healthy female participants.

All participants will have 2 screening visits with the first to evaluate the health of the participant and the second visit to undergo an LDI assessment to ensure a response of at least 100% increase in DBF between pre- and post-CA challenge. Following a screening period of up to 28 days, eligible participants will be confined to the clinical research unit from Day 1 until all assessments are completed on Day 2 of each dosing period.

As summarized in Table 1, each participant will be randomly assigned to 1 of 4 treatment sequences, with a ratio of 3 LY3526318: 1 placebo. Each participant will receive 3 doses of LY3526318 and 1 dose of placebo in a crossover manner, with at least 6 days of washout between doses. The planned dose levels of LY3526318 are anticipated not to exceed the maximum administered dose in the SAD portion of Study CVAA.

Table 1 Treatment Sequence

Sequence	N	Period 1	Period 2	Period 3	Period 4
P132	4	P	D1	D3	D2
12P3	4	D1	D2	P	D3
231P	4	D2	D3	D1	P
3P21	4	D3	P	D2	D1

During each visit (screening and study periods), each patient will undergo at least 30 minutes acclimatization and placement of 3 rubber O-rings on the volar surface of the forearm. Prior to study drug administration, a pre-drug DBF will be collected without CA. For each time point following study drug administration, pre-CA measurements will be performed for the areas defined by the rings within 10 minutes before CA application. After the pre-CA measurements, a 20 µL topical dose of 10% CA will be applied in the proximal O-ring of the participant's forearm. Using the same procedure, a 20 µL topical dose of 3% CA will be applied in the medial ring, followed by a 20 µL topical dose of the vehicle solution to the distal ring. LDI/LSCI measurements will again be performed approximately 20 minutes after CA and vehicle applications. Specific details of the procedure will be agreed upon and documented between the sponsor and investigator and research staff operating the equipment.

All assessments will be performed as defined in Schedule of Activities (Appendix 2: Schedule of Assessments).

All participants will attend a safety follow-up visit about 7 days following the last dose of study drug.

6.1 Sample Size Considerations

The sample size is justified based on the statistical power to meet the primary endpoint of DBF measurements from LDI assay at t_{max}. The power calculation used 10% CA-induced absolute DBF in comparison between LY3526318 and placebo arms. For a 20% reduction in DBF (assuming mean observed placebo DBF of 444.3 arbitrary perfusion units (PU) with standard deviation (SD) of 55.1 PU) and a significance level of 0.05, a paired t-test with 16 patients results in 98% power to reject the null hypothesis. Incorporating a Bonferroni adjustment to account for multiplicity (changing the significance level to 0.05/3) lowers the power slightly to 96%.

6.2 Randomization

A randomization schedule will be prepared by the Biostatistics Department of PRA. Subjects (numbered 01-16) will be assigned to one of the 4 sequences. The subjects are to be assigned to a treatment sequence in blocks of 4 (with subject numbers 01-04, 05-08, 09-12 and 13-16), with each of the 4 sequences assigned once in each of the 4 blocks.

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

There will be no interim analyses or summaries of data provided prior to the delivery of the full set of post-lock tables, figures and listings (TFLs).

7.3 Final Analysis

Draft TFLs will be provided with the draft CSR. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the final 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 summaries, all descriptive statistics will be presented to the same number of decimal places as the original data.

Frequency percentages will be presented with one decimal.

Percentage change for PD measurements will be presented with one decimal.

Derived parameters will generally be presented with three significant figures.

P-values will be reported to four decimal places; p-value less than 0.0001 will be reported as “<0.0001”.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

Missing start or end times for AEs will be imputed as described in 18.1.1.

PK concentrations below the quantifiable limit (BQL) will be replaced as described in 16.2.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, 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. When there is a difference between the descriptions of categories in the eCRF and the database, the description in the database will be used.

9.1.4 Pooling

Summary statistics will be calculated by treatment (and time point, if applicable).

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 study drug administration in each period. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping

Label	Grouping
Treatment	Placebo LY3526318 x mg LY3526318 y mg LY3526318 z mg
Treatment abbreviated	P D1 D2 D3
Treatment numeric	0 1 2 3

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation	Note
Change from Baseline	All	Post-dose Observation minus Baseline Observation	Within period
Analysis Study Day (Prior to Dose)	All	Date of Measurement minus Dose Date	Within period
Analysis Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1	Within period

9.2.4 QC

The 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 end point related to the primary objective of this study is CA-induced DBF, the dataset considered critical are pharmacodynamic data (ADPD). Therefore this dataset will be double programmed per the QC Plan.

9.2.5 ADaM Datasets and Metadata

Analysis datasets that will be created are subject level (ADSL), AE (ADAE), clinical laboratory (ADLB), electrocardiogram (ADEG), vital signs (ADVS), pharmacokinetic concentrations (ADPC) and pharmacodynamic DBF results (ADPD).

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

A define.xml file version 2 will be created. 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.).

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

Significance testing will be 1-sided at the significance level of 0.05/3 for the primary statistical analysis.

9.5 TFL Layout

Report layout will be according to the PRA EDS – ICH E3 compliant – 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: A4
- Data in listings will be sorted by subject number and time point.
- Data In tables will be sorted by treatment and time point.
- 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 9.2.2.

10.0 Analysis Sets

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

10.1 Randomized Analysis Set

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

10.2 Safety Analysis Set

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

10.3 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set (PDAS) will consist of all subjects who receive LY3526318 or placebo at least once and have at least one reliable post-dose PD measurement (LDI or LSCI).

Available data from drop-outs will be included in summaries.

Data from drop-outs will be included in statistical analysis if data are available for at least the placebo and one active treatment.

11.0 Subject Disposition

The number and percentage of subjects randomized, dosed in Period 1, 2, 3 and 4, included in the SAF, in the PDAS, completing the study, withdrawing from the study prematurely and a breakdown of the corresponding reasons for withdrawal will be presented by treatment sequence and overall. The denominator for the percentage is the number of subjects randomized.

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 overall. 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 SAF and PDAS (if different).

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.

Serology (Hepatitis B surface antigen, Hepatitis C antibody and human immunodeficiency virus) will be listed.

Pregnancy (beta subunit of human chorionic gonadotropin) will be listed.

14.0 Concomitant Medications

Concomitant medication will be listed. Medications are categorized by data management as prior or concomitant. This information will also be listed.

Concomitant medications will be coded according to the World Health Organization – Drug Dictionary Enhanced (WHO-DDE) (Version Global B3 2018Sep01 or later).

15.0 Treatment Compliance and Exposure

Exposure data will be listed by subject.

16.0 Pharmacokinetic Analyses

Samples are collected at pre-dose, and at 3 h (the estimated t_{max}) and 24 h post-dose. PK parameters will not be derived.

16.1 Pharmacokinetic Variables

PK concentrations of LY3526318 and the main (active) metabolite M6 will be analyzed in plasma.

16.2 Pharmacokinetic Summaries

Plasma concentrations for LY3526318 and M6 BQL will be set to ½ lower limit of quantification (LLOQ) in the computation of mean concentration values. Descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum) will be used to summarize the plasma concentrations by treatment at each scheduled time point. If over ½ the subjects for a specific combination of time point, treatment and analyte have values BQL then the descriptive statistics of that specific combination 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.

All individual subject plasma concentration data will be listed together with the descriptive statistics.

17.0 Pharmacodynamic Analysis

17.1 Pharmacodynamic Variables

PD assessments will be DBF measured by two methods, LDI and LSCI. For time points with a pre- and post-CA measurement available, the percentage change will be calculated.

17.2 Pharmacodynamic Summaries

17.2.1 Descriptive Summary

The individual DBF measurements absolute values (all 5 time points) and percentage change from pre-CA (for post-CA at 3 and 24 hours post study drug) will be listed and summarized descriptively by treatment, timepoint, CA concentration and method.

The individual percentage change from pre-CA will be graphically presented with the treatments combined in a plot by subject, CA concentration and method. Additionally, combined individual plots will be presented, with all individual percentage change combined in a plot by treatment, CA concentration and method. The arithmetic mean (±SD) will be graphically presented with the treatments combined in a plot, by CA concentration and method.

17.2.2 Statistical Analysis

An analysis of variance (ANOVA) will be performed on the percentage change (pre- to post-CA) at time points 3 h and 24 h post-dose using PROC MIXED in SAS. The percentage change will be used untransformed in the analysis. The model will include fixed effects for treatment, period, sequence, time and treatment*time interaction and a random effect for subject within sequence. The analysis will be done for each, method and CA concentration separately. From this model the least-squares means (LSMeans) for each treatment (including placebo) and the difference of the LSMeans for each of the active treatments with placebo at 3 h and at 24 h post-dose and the corresponding P value will be estimated for each method and CA concentration.

In the summary of the statistical analysis, it will be indicated that the result for LDI, 3 hours post-dose is the primary end point.

In SAS code:

```
proc mixed data=dbf;
   by CAconc method;
   class subject trtan time            period seq;
   model pchg =  trtan time trtan*time period seq;
   random subject(seq);
   lsmeans trtan*time ;
   /*estimates*/
run;
quit;
```

For each of the active dose levels and CA concentrations, a decrease relative to placebo of the percentage change (pre- to post-CA) with a P value below (0.05/3) will be considered statistically significant.

Additionally, the same model (with fixed effects for treatment, period, sequence, time and treatment*time interaction and a random effect for subject within sequence) will be applied to the absolute values for each method and CA concentration separately, using data from all time points (i.e. pre study drug, 3 h pre- and post-CA, 24 h pre- and post-CA). From this model, using the absolute values, LSMeans and the differences with 90% CI and P-value will be estimated for each method and CA concentration for the following comparisons:

#	LSMean (absolute value) of	Compared with LSMean (absolute value) of
1	D1 post-CA at 3 h	Placebo post-CA at 3 h
2	D2 post-CA at 3 h	Placebo post-CA at 3 h
3	D3 post-CA at 3 h	Placebo post-CA at 3 h
4	D1 post-CA at 24 h	Placebo post-CA at 24 h
5	D2 post-CA at 24 h	Placebo post-CA at 24 h
6	D3 post-CA at 24 h	Placebo post-CA at 24 h
7	Placebo pre-CA at 3 h	Placebo pre study drug at 0 h
8	D1 pre-CA at 3 h	D1 pre study drug at 0 h
9	D2 pre-CA at 3 h	D2 pre study drug at 0 h
10	D3 pre-CA at 3 h	D3 pre study drug at 0 h
11	Placebo pre-CA at 24 h	Placebo pre study drug at 0 h
12	D1 pre-CA at 24 h	D1 pre study drug at 0 h
13	D2 pre-CA at 24 h	D2 pre study drug at 0 h
14	D3 pre-CA at 24 h	D3 pre study drug at 0 h

In SAS code:

```
proc mixed data=dbf;
   by CAconc method;
   class subject trtan time            period seq;
   model aval =  trtan time trtan*time period seq;
   random subject(seq);
   lsmeans trtan*time ;
   /*estimates*/
run;
quit;
```

18.0 Safety Analyses

18.1 Safety Variables

The following safety variables will be summarized:

- AEs
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Pulse rate
  - Temperature
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - QTc (Fredericia) Interval
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis

18.1.1 Adverse Events

All AE summaries will include only TEAEs. TEAEs are those which start or worsen relative to the pretreatment state 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.

TEAEs occurring following dosing in a specific period but before dosing in the next period will be attributed to that specific period. If the time is missing for an AE on a dosing day then the AE will be attributed to the treatment given on that day.

A breakdown of the number of events, number and percentage of subjects reporting TEAEs, categorized by SOC, PT and overall, coded according to MedDRA (Version 21.1 or latest version), will be presented by treatment and all active treatments combined and overall. This summary will be presented for all TEAEs and for TEAEs considered related to the study medication.

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 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

18.1.2 Deaths and Serious Adverse Events

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

18.1.3 Laboratory Data

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

All laboratory data 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 will be provided to summarize continuous laboratory results of clinical chemistry and hematology (observed and derived absolute changes from baseline) by treatment and scheduled time.

18.1.4 Vital Signs

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

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

Scatterplots will be presented with the time-matched individual QTcF (absolute and absolute change from baseline) value vs PK concentration (both analytes). Separate plots for absolute and change from baseline QTcF and separate plots for PK analytes, i.e. 4 plots in total.

18.1.6 Physical Examinations

The findings and changes from previous visits for physical examination will be listed.

18.1.7 Body Weight

The results of the body weight measurements will be listed. The results at screening are listed as demographic data, but will also be listed here for completeness.

18.1.8 C-SSRS

The results of the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire will listed.

19.0 References

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

Clinical Study Protocol. A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Oral Single-Doses of LY3526318 on Cinnamaldehyde-Induced Dermal Blood Flow in Healthy Females. Version 1.0, Final, 15 Nov 2018.

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
CA	cinnamaldehyde
CDISC	Clinical Data Interchange Standard Consortium
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
DBF	Dermal Blood flow
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LDI	Laser doppler imaging
LLOQ	Lower limit of quantification
LSCI	Laser Speckle contrast imaging
LSMeans	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PDAS	Pharmacodynamic Analysis Set
PK	Pharmacokinetic
PU	Perfusion units
QA'd	Quality assured
QC'd	Quality controlled
RAND	Randomized Analysis Set
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAE	Serious adverse event
SD	Standard deviation

SDTM	Study data tabulation model
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WHO-DDE	World Health Organization – Drug Dictionary Enhanced

Appendix 2: Schedule of Assessments

	S		Treatment Period 1				Treatment Period 2				Treatment Period 3				Treatment Period 4			FU	ED[d]
Study Day	≤28		-1[b]	1	2	8	14[b]	15	16	22	28[b]	29	30	36	42[b]	43	44	50	-
Visit Window (days)	-		-	-	-	±1	-	-	-	±1	-	-	-	±1	-	-	-	±2	-
Visit	1[a]	2[a]	3[c]			4	5[c]			6	7[c]			8	9[c]			10	
Admit to CRU			X				X				X				X				
Discharge from CRU					X				X				X				X		
CRU visit	X	X				X				X				X				X	X
Informed consent	X																		
Medical history	X																		
Height	X																		
Weight	X		X															X	X
Physical examination	C		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	C	C
Urine drug screen and ethanol test	X		X				X				X				X			X	X
Hematology and clinical chemistry	X			P	24h			P	24h			P	24h			P	24h	X	X
Urinalysis[e]	X			P														X	X
β-hCG pregnancy test	X		X			X	X			X	X			X	X			X	X
C-SSRS	X		X				X				X				X			X	X
Vital signs including temperature	X			P and 3h	24h			P and 3h	24h			P and 3h	24h			P and 3h	24h	X	X
ECG[f]	X			P and 3h	24h			P and 3h	24h			P and 3h	24h			P and 3h	24h	X	X
Randomization				X															
Study drug administration[g]				X				X				X				X			
PK blood sample[h]				P and 3h	24h	X		P and 3h	24h	X		P and 3h	24h	X		P and 3h	24h	X	X
DBF by LDI[a,i]		X																	
DBF by LDI and LSCI[i]				P and 3h	24h			P and 3h	24h			P and 3h	24h			P and 3h	24h		
AE / Con Med	← X →																		

Abbreviations: AE = adverse events; C = compete physical examination; Con Med = concomitant medications CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; DBF = dermal blood flow; ECG = electrocardiogram; ED = early discontinuation; FU = safety follow-up; h = hour; LSCI = laser speckle contrast imaging; LDI = laser Doppler imaging; P = pre-dose assessment; PK = pharmacokinetic; S = Screening.

Note: In the event that assessments are planned for the same time, assessments should be conducted in following order: LSCI DBF assessment, LDF DBF assessment, PK sample, and ECG/vital signs. The PK sample should be collected as soon as the LDI/LSCI DBF assessment is completed. The ECG and vital signs measurement should be obtained at least 30 minutes after the PK sample is drawn.

a Screening visits will be performed within 28 days before the administration of first dose. All participants will have 2 screening visits with the first to evaluate the health of the participant and the second visit to undergo the LDI DBF assessment.
b Can be performed on a day prior to dosing or pre-dose on day of dosing.
c All participants will remain in the CRU until completion of all procedures that occur the day following each dose.
d Participants who discontinue the study prior to study completion will complete the ED visit procedures.
e A standard urine dipstick may be used.
f A single 12 lead ECGs will be obtained in the supine position after at least 10 minutes rest.
g Study drug will be administered in a fasting state (8 hours pre-dose until 4 hours post-dose). The exact time study drug is administered will be recorded.
h The timing of PK sample collections may be adjusted based on clinical needs. The exact sample collection dates and times must be recorded.
i All participants will have an LDI and LSCI procedure with cinnamaldehyde challenge to measure DBF at stipulated time points. The pre-dose measurement will include at least 30 minutes of acclimatization, followed by a dermal blood flow measurement, without cinnamaldehyde application. Each post-dose measurements will include at least 30 minutes of acclimatization, followed by a pre-cinnamaldehyde dermal blood flow measurement (about 10 minutes before cinnamaldehyde application). Next, cinnamaldehyde will be applied and a post-cinnamaldehyde measurement at 20 minutes following the cinnamaldehyde application will be performed. The LDI assessment will be performed following completion of LSCI assessment.

Appendix 3: List of End of Text Outputs

TFLs listed below can also be used in the body of the CSR.

Output	Title	Analysis Set
Section 12.1 Demographic and Other Baseline Data		
Section 12.1.1 Demographic Data		
Listing 12.1.1.1	Subject Randomization and Treatment Assignment	RAND
Table 12.1.1.2	Summary of Subject Disposition	RAND
Table 12.1.1.3	Summary of Demographics (Safety Analysis Set)	SAF
Table 12.1.1.4	Summary of Demographics (PD Analysis Set) (This table may be combined with 12.1.1.3 if PDAS is equal to SAF)	PDAS
Listing 12.1.1.5	Subject Demographics	SAF
Listing 12.1.1.6	Analysis Sets	RAND
Section 12.1.1 Other Baseline Data		
Listing 12.1.2.1	Medical History	SAF
Listing 12.1.2.2	Prior and Concomitant Medications	SAF
Listing 12.1.2.3	Result of Serology Tests	SAF
Table 12.1.2.4	Result of Pregnancy Tests	SAF
Section 12.2 Compliance Data		
Listing 12.2.1	Study Dates	SAF
Listing 12.2.2	Subject Disposition	SAF
Listing 12.2.3	Study Drug Administration	SAF
Section 12.3 Safety Data		
Section 12.3.1 Adverse Events		
Table 12.3.1.1	Table of Deaths and Other Serious Adverse Events	SAF
Listing 12.3.1.2	Adverse Events Leading to Withdrawal	SAF
Listing 12.3.1.3	Adverse Events	SAF
Table 12.3.1.4	Summary of All Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF
Table 12.3.1.5	Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF
Table 12.3.1.6	Summary of Treatment-Emergent Adverse Events by Treatment, Relationship and Severity	SAF
Section 12.3.2 Clinical Laboratory		
Listing 12.3.2.1	Clinical Laboratory Results - Chemistry	SAF
Listing 12.3.2.2	Clinical Laboratory Results - Hematology	SAF

Listing 12.3.2.3	Clinical Laboratory Results - Urinalysis	SAF
Listing 12.3.2.4	Clinical Laboratory Results - Alcohol and Drug Screen Test Results	SAF
Listing 12.3.2.5	Clinical Laboratory Results - Comments	SAF
Table 12.3.2.6	Summary of Clinical Laboratory Data - Clinical Chemistry	SAF
Table 12.3.2.7	Summary of Clinical Laboratory Data - Hematology	SAF
Table 12.3.2.8	Listing of Abnormal Laboratory Values	SAF
Section 12.3.3 Vital Signs Data		
Listing 12.3.3.1	Vital Signs	SAF
Table 12.3.3.2	Summary of Vital Signs	SAF
Section 12.3.4 ECG Data		
Listing 12.3.4.1	12-Lead Electrocardiogram Results - Individual Parameters	SAF
Listing 12.3.4.2	Lead Electrocardiogram Results - Investigator's Interpretation and Specification of Abnormalities	SAF
Table 12.3.4.3	Summary of 12-Lead Electrocardiogram	SAF
Figure 12.3.4.4	QTcF vs LY3526318 and M6 Plasma Concentrations (absolute and change from baseline)	SAF
Section 12.3.5 Other Safety Data		
Listing 12.3.5.1	Physical Examination Findings and Changes	SAF
Listing 12.3.5.2	Body Weight	SAF
Listing 12.3.5.3	C-SSRS Results	SAF
Section 12.4 Pharmacokinetic and Pharmacodynamic Data		
Section 12.4.1 Plasma Pharmacokinetic Data		
Listing 12.4.1.1	LY3526318 and M6 Plasma Concentrations, Sampling Time Deviations and Comments (by treatment and time point)	SAF
Table 12.4.1.2	Descriptive Statistics of LY3526318 Plasma Concentrations	SAF
Table 12.4.1.3	Descriptive Statistics of M6 Plasma Concentrations	SAF
Section 12.4.2 Plasma Pharmacodynamic Data		
Listing 12.4.2.1	Individual LDI and LSCI Results and Time Deviations and Comments	SAF
Table 12.4.2.2	Descriptive Statistics of LDI-DBF	PDAS
Table 12.4.2.3	Descriptive Statistics of LSCI-DBF	PDAS
Table 12.4.2.4	Statistical Analysis (ANOVA) of LDI-DBF (% pre- to post-CA)	PDAS
Table 12.4.2.5	Statistical Analysis (ANOVA) of LSCI-DBF (% pre- to post-CA)	PDAS
Table 12.4.2.6	Statistical Analysis (ANOVA) of LDI-DBF (absolute value)	PDAS

Table 12.4.2.7	Statistical Analysis (ANOVA) of LSCI-DBF (absolute value)	PDAS
Figure 12.4.2.8	Arithmetic Mean (±SD) LDI-DBF versus Time on Linear Scale	PDAS
Figure 12.4.2.9	Arithmetic Mean (±SD) LSCI-DBF versus Time on Linear Scale	PDAS
Figure 12.4.2.10	Combined Individual LDI-DBF versus Time On Linear Scale	PDAS
Figure 12.4.2.11	Combined Individual LSCI-DBF versus Time On Linear Scale	PDAS
Figure 12.4.2.12	Individual LDI-BDF versus Time On Linear Scale	SAF
Figure 12.4.2.13	Individual LSCI-BDF versus Time On Linear Scale	SAF

20.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
10-Dec-2019	PPD	First version, based on EDSREP 009 T 01 G
21-Dec-2019		Comments internal review (PRA)
27-Jan-2020		Comments sponsor (Eli Lilly)
06-Feb-2020		Comments sponsor
11-Feb-2020		Finalizing