Statistical Analysis Plan: J4L-MC-KMAA

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3872386 in Healthy Participants, a Multiple-Ascending Dose Study of LY3872386 in Patients with Atopic Dermatitis, and an Open-Label Multiple-Dose Evaluation of the Safety and Tolerability of Prednisone in Healthy Participants.

NCT06119529

Approval Date: 31-Oct-2023

STATISTICAL ANALYSIS PLAN

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3872386 in Healthy Participants, a Multiple-Ascending Dose Study of LY3872386 in Patients with Atopic Dermatitis, and an Open-Label Multiple-Dose Evaluation of the Safety and Tolerability of Prednisone in Healthy Participants.

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Version: 1.0
Statistical Analysis Plan Date: 30 October 2023

Investigational Medicinal Product: LY3872386

Protocol Reference: J4L-MC-KMAA
Fortrea Study: 8524153

Clinical Phase I

1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures, and listings [TFLs]).

Δ	Change from baseline
ΔΔ	Placebo-corrected change from baseline
$\%AUC_{(tlast-\infty)}$	fraction of AUC(0-∞) extrapolated
AD	Atopic dermatitis
ADA	Anti-drug antibodies
ADC	Antibody drug conjugate
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the concentration versus time curve
AUC_{0-12}	Area under the concentration versus time curve from time 0 to 12 hours post dose
AUC_{0-t}	Area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration
AUCτ	Area under the concentration versus time curve during one dosing interval
$AUC_{0-\infty}$	Area under the concentration versus time curve from time 0 to infinity
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CL_{ss}/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CCI	[redacted]

CV	Coefficient of variation
DLQI	Dermatology Life Quality Index
DMP	Data Management Plan
CCI	[redacted]
ECG	Electrocardiogram
FAS	Full analysis set
CCI	[redacted]
ICH	International Conference on Harmonization
CCI	[redacted]
[redacted]	[redacted]
IV	Intravenous
LLOQ	Lower limit of quantification
LS	Least square
LY	LY3872386
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRE	Magnetic resonance elastography
NRS	Numeric rating scale
CCI	[redacted]
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Oral administration
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
QD	Once daily
QTcF	QT interval corrected using Fridericia's formula
RO	Receptor occupancy
SAD	Single ascending dose

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
CCI	[redacted]
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TEAE	Treatment-emergent adverse event
TE ADA	Treatment-emergent anti-drug antibodies
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
CCI	[redacted]
[redacted]	[redacted]
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z/F	Apparent total body clearance of drug calculated after extra-vascular administration
WBC	White blood cell
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 01 September 2023).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to first participant visit. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

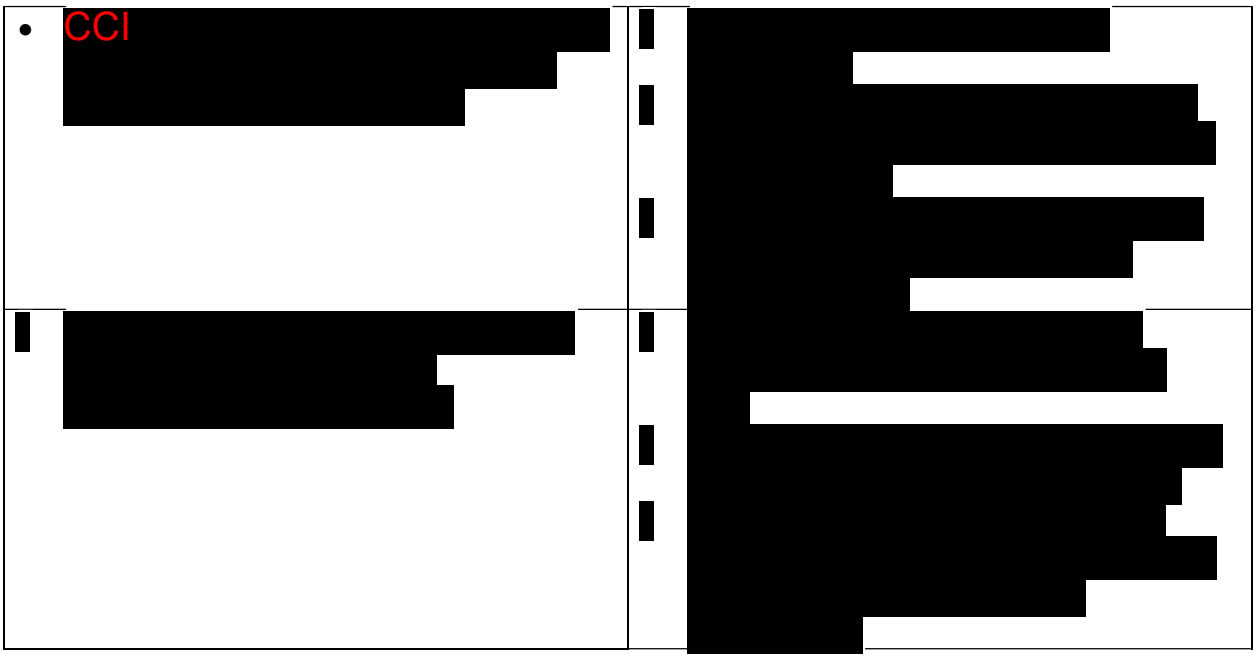
This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To characterize the safety of LY3872386 after single dose administration in healthy participants and after repeat dose administration in patients with atopic dermatitis (AD).	• Number and incidence of adverse events (AEs), treatment-emergent AEs (TEAEs), and serious AEs (SAEs)
• To characterize the safety of prednisone in healthy participants receiving multiple oral administration (PO) once daily (QD) doses in various dosing groups.	• Number and incidence of AEs, TEAEs, and SAEs

Objectives	Endpoints
Secondary	
• To characterize the PK of LY3872386, total antibody, and the LY3558533 (free payload) following single dose administration in healthy participants and after repeat dosing in patients with AD.	• Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) of LY3872386, total antibody, and LY3558533 (free payload)
• To characterize the PK of prednisone in healthy participants receiving multiple PO QD doses in various dosing groups.	• C_{max} and AUC of prednisone and prednisolone
CCI	



5. STUDY DESIGN

Study J4L-MC-KMAA (KMAA) is a first-in-human trial designed to characterize the safety and tolerability of LY3872386 as well as the PK of LY3872386, total antibody, and LY3558533 (free payload) in healthy participants and in patients with AD. Additionally, this study will assess the safety, PK, tolerability, and PD of various dose levels of prednisone in healthy participants. The study will enroll participants of any ethnicity. CCI

The study will be conducted in 3 parts as follows:

- Part A (SAD of LY3872386) will characterize the safety, tolerability, PK, and PD after single intravenous (IV) and SC dose administration of LY3872386 in healthy participants.
- Part B (multiple ascending dose [MAD] of LY3872386) will characterize the safety, tolerability, PK, and PD after multiple SC and/or IV dose administrations of LY3872386 in patients with AD.
- Part C CCI will assess the safety, tolerability, PK, and PD after repeat PO administration of prednisone in healthy participants.

The study schema demonstrating the relationship among Parts A, B, and C is shown below in

Figure 1.

Figure 1: J4L-MC-KMAA Study Schema

Screening Period

Screening may occur up to 35 days prior to Day 1 of the study. After obtaining informed consent, participants will be screened for eligibility as detailed in the protocol.

Participants who are not enrolled within 35 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. The assessments will be repeated at the discretion of the investigator.

Treatment Period and Visit Frequency

Part A: SAD of LY3872386 in Healthy Participants

Part A will be a SAD study of LY3872386 in healthy participants and will be comprised of 8 cohorts. SAD Cohorts 1 to 5 will consist of CCI healthy participants each who will be randomly assigned to receive LY3872386:PBO in a CCI manner. SAD Cohorts 6 to 8 will consist of CCI participants who will be randomly assigned to receive LY3872386:PBO in a CCI manner. See Table 1 for further details.

The planned doses are CCI mg IV (Cohort 1), CCI mg IV (Cohort 2), CCI mg IV (Cohort 3), CCI mg IV (Cohort 4), CCI mg SC (Cohort 5), CCI mg IV (Cohort 6), CCI mg SC (Cohort 7), and CCI mg IV (Cohort 8). The study intervention will be administered as a single dose on Day 1, followed by a 12-week follow-up period. Dose escalation will be based on the review of available data from the ongoing cohorts. Refer to the protocol for further details on dose escalation.

CCI

Refer to the protocol for details on administration and data review prior to dosing.

Participants will be inpatient for CCI, followed by visits at regular intervals. Participants will be monitored for safety, CCI, and samples will be collected as outlined in the protocol. Participants will be discharged from the clinical research unit (CRU) CCI after all the study assessments have been completed during the treatment period and in agreement with the investigator.

Part B: MAD of LY3872386 in Patients with Atopic Dermatitis

Part B will be a MAD study in patients with AD and will be comprised of 2 cohorts. Each cohort will consist of at least CCI randomized participants.

The planned doses are CCI mg IV or SC (Cohort 1) and CCI mg IV or SC (Cohort 2). The study intervention will be administered CCI) for up to 12 weeks. See Table 1 for further details.

Participants will be followed on an outpatient basis by visits at regular intervals.

Refer to the protocol for details on administration, commencement of Part B, and data review prior to dosing.

Part C: Open-label Multiple Dose of Prednisone in Healthy Participants

Part C will be an open-label multiple dose study of prednisone in 1 cohort of healthy participants. Participants will receive either CCI mg of prednisone (Table 2)

- CCI mg or CCI mg prednisone PO QD for a total of CCI doses
  - CCI
- CCI mg prednisone PO QD for a total of CCI doses
  - CCI

Refer to the protocol for details on administration and the commencement of Part C.

For all study parts

The timings and procedures are outlined in the protocol. If the investigator deems it necessary, participants may remain in the CRU for a longer duration. Any changes to the planned discharge day will be made in consultation with the sponsor.

Follow-up Period

Participants will be required to return to the CRU for clinical assessments and blood samples on an outpatient basis (see protocol). The final follow-up visit will be approximately 12 weeks after the single dose of the study intervention in Part A, 14 weeks after the last dose of the study intervention in Part B, and 2 weeks after the last dose of prednisone in Part C.

Table 1: Summary of Participants in Cohorts Dosed with LY3872386

Part A: SAD of LY3872386 in Healthy Participants[a]					
Cohort #	**Planned Dose / Administration Route**	**Number of Planned Non-Japanese / Non-Chinese Participants**	**Number of Planned Japanese Participants**	**Number of Planned Chinese Participants**	**Total Number of Planned Completers**

		LY	PBO	LY	PBO	LY	PBO	
Cohort 1	CCI mg IV	CCI LY: CCI PBO						CCI per cohort
Cohort 2	CCI mg IV							
Cohort 3	CCI mg IV							
Cohort 5	CCI mg SC							
Cohort 4[b]	CCI mg IV	CCI						
Cohort 6[c]	CCI mg IV							
Cohort 7[c]	CCI mg SC	CCI						CCI per cohort
Cohort 8[c]	CCI mg IV							
Part B: MAD of LY3872386 in Patients with AD								
Cohort #	**Planned Dose / Administration Route**	**Number of Planned Patients**						**Total Number of Planned Randomized Patients**
Cohort 1	CCI mg IV or SC	CCI LY: CCI PBO						CCI
Cohort 2	CCI mg IV or SC							

Abbreviations: AD = atopic dermatitis; IV = intravenous; LY = LY3872386; MAD = multiple-ascending dose, PBO = placebo; PO = oral administration; SAD = single-ascending dose; SC = subcutaneous.
[a] Sentinel dosing will be used.
[b] Sentinel pair must be non-Japanese and non-Chinese participants OR Sentinel pair must be mixed ethnicities (CCI non-Japanese/non-Chinese participant and CCI Japanese participant).
[c] Sentinel pair must be non-Japanese and non-Chinese participants.

Table 2: Summary of Participants Dosed with Prednisone

Part C: Multiple Doses of Prednisone in Healthy Participants		
Dosing Group	**Planned Dose / Administration Route**	**Total Number of Planned Completers**
Group 1	CCI mg PO	CCI
Group 2	CCI mg PO	CCI
Group 3	CCI mg PO	CCI

Abbreviation: PO = oral administration

6. BLINDING

Parts A and B are randomized participant- and investigator-blind. All measures possible must be taken to maintain the blind; access to the blinding information will be restricted to authorized personnel as described in the protocol. Staff who prepare the study intervention will not be blinded to treatment allocation.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. In such cases, the unblinding is to be conducted according to the protocol.

The Fortrea biometrics and Eli Lilly study teams will be unblinded throughout the study.

Part C is a non-randomized, open-label study.

7. TREATMENTS

The following is a list of the study treatment names that will be used in the TFLs.

For each part, the data from PBO groups will be pooled across cohorts as 1 PBO group.

Part A:

Cohort	Study Treatment Name	Treatment order in TFL
All	Placebo IV	1
	Placebo SC	2
1	CCI mg LY3872386 IV	3
2	CCI mg LY3872386 IV	4
3	CCI mg LY3872386 IV	5
4	CCI mg LY3872386 IV	6
5	CCI mg LY3872386 SC	7
6	CCI mg LY3872386 IV	8
7	CCI mg LY3872386 SC	9
8	CCI mg LY3872386 IV	10

Abbreviations: IV = intravenous; SC = subcutaneous

Part B:

Cohort	Study Treatment Name	Treatment order in TFL
All	Placebo	1
1	CCI mg LY3872386 TBD (IV or SC) TBD (CCI or CCI)	2
2	CCI mg LY3872386 TBD (IV or SC) TBD (CCI or CCI)	3

Abbreviations: IV = intravenous; CCI SC = subcutaneous

Part C:

Group	Study Treatment Name	Treatment order in TFL
1	CCI mg prednisone PO QD	1
2	CCI mg prednisone PO QD	2
3	CCI mg prednisone PO QD	3

Abbreviations: PO = oral administration; QD = once daily

8. SAMPLE SIZE JUSTIFICATION

The study will enroll up to CCI evaluable participants (CCI healthy volunteers and up to CCI patients with AD).

CCI [redacted]

For purposes of this study, a participant completes the study when all scheduled procedures shown in the protocol have been finished. Participants who withdraw before completing all dosing administrations may be replaced. A replacement participant will complete the entire study period. Participants who discontinued the study following the required dose administration(s) but before completing may be replaced at the discretion of the sponsor and investigator. CCI [redacted]

9. DEFINITION OF ANALYSIS POPULATIONS

The "Enrolled" population will consist of all participants assigned to treatment, regardless of whether they take any doses of LY, Prednisolone, or PBO, or whether they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.

The "FAS (Full Analysis Set)" population will consist of all randomized participants.

The "mITT (Modified Intent-to-Treat)" population will consist of all randomized participants who receive at least one dose of LY, Prednisolone, or PBO. Participants will be analyzed according to the treatment to which they were assigned (regardless of whether the participant fails to receive the correct treatment, or otherwise fails to follow the protocol).

The "Safety" population will consist of all randomized participants who received at least one dose of LY, Prednisolone, or PBO. Participants will be included according to the treatment they actually received, regardless of whether they have completed all protocol requirements.

The "Pharmacokinetic" population will consist of all enrolled participants who received at least one dose of LY or Prednisolone and have evaluable PK data. For Part C with oral dosing, participants may be excluded from the PK summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

The "Pharmacodynamic" population will consist of all participants who received at least one dose of LY, Prednisolone, or PBO and have evaluable PD data. For Part C with oral dosing, participants may be excluded from the PD summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median t_{max}.

The "Safety/Pharmacokinetic" population will consist of all participants in both the Safety and PK population with at least 1 pair of PK and electrocardiogram (ECG) data from the same timepoint, as well as participants in the Safety Population who received PBO.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

10. STATISTICAL METHODOLOGY

10.1 General

For Part A, TFLs may be presented separately by race and ethnicity (e.g., Overall, Japanese, Chinese, and non-Japanese/non-Chinese), as appropriate.

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum, and number of observations; for log-normal data (e.g., the PK parameters: AUCs and C_{max}) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

For change from baseline summary statistics, each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at that time point. The individual participants' change from baseline values will be used to calculate the summary statistics (arithmetic mean, arithmetic SD, median, minimum, maximum, and number of observations) using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

10.2 Demographics and Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized by part and treatment and listed. All other demographic variables will be listed only.

In Part B, baseline disease characteristics CCI [redacted] will also be summarized by treatment and listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

The following PK parameters will be determined using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or higher):

Plasma concentrations of LY3872386, total antibody, LY3558533 (free payload) will be used to determine the following PK parameters for Parts A and part B, where possible:

For Part A - SAD (Cohorts 1 to 8):

Parameter	Units[a]	Definition
$AUC_{(CCI)}$	µg.h/mL	area under the concentration versus time curve from time 0 to CCI hours post dose.
$AUC_{(CCI)}$	µg.h/mL	area under the concentration versus time curve from time 0 to CCI hours post dose.
$AUC_{(0-t)}$	µg.h/mL	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration.
$AUC_{(0-\infty)}$	µg.h/mL	area under the concentration versus time curve from time 0 to infinity
$\%AUC_{(tlast-\infty)}$	%	fraction of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	h	time of the maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (for LY3872386 only)
V_z/F	L	apparent total body clearance of drug calculated after extra-vascular administration (for LY3872386 only)
CL	L/h	total body clearance of drug calculated after intravenous administration (for LY3872386 only)
Vz	L	Volume of distribution during terminal phase (LY3872386 IV dosing)
F	%	bioavailability of drug. Fraction of extravascular dose reaching the general circulation compared to an IV administration

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.

For Part B - MAD (Cohorts 1 and 2), Profile Day 1 and Day 85:

Parameter	Units[a]	Definition
$AUC_{(0-t)}$	µg.h/mL	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration. [b]
AUC_{τ}	µg.h/mL	area under the concentration versus time curve during one dosing interval
$AUC_{(0-\infty)}$	µg.h/mL	area under the concentration versus time curve from time 0 to infinity [b]
$\%AUC_{(tlast-\infty)}$	%	fraction of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	h	time of the maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (for LY3872386 only)
V_z/F	L	apparent total body clearance of drug calculated after extra-vascular administration (for LY3872386 only)
CL_{ss}/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (for LY3872386 only)
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration (for LY3872386 only)
CL	L/h	total body clearance of drug calculated after intravenous administration (for LY3872386 only)
V_z	L	volume of distribution during the terminal phase after intravenous administration (for LY3872386 only)
CL_{ss}	L/h	total body clearance of drug at steady state calculated after intravenous administration (for LY3872386 only)
V_{ss}	L	volume of distribution at steady state following intravenous administration (for LY3872386 only)
RA_{AUC}		accumulation ratio calculated for steady state AUC τ versus Day 1
RA_{cmax}		accumulation ratio calculated for steady state Cmax versus Day 1

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
CL/F, Vz/F, CL, Vz will be reported for profile day 1, whereas CLss/F, Vss/F, CLss, Vss will be reported for profile day 85.

Plasma concentrations of prednisone and prednisolone will be used to determine the following PK parameters for Part C, where possible:

For Part C (Day 1, Day 7, and Day 30):

Parameter	Units[a]	Definition
AUC_{τ}	µg.h/mL	area under the concentration versus time curve during one dosing interval
$AUC_{(0-t)}$	µg.h/mL	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration.
$AUC_{(0-\infty)}$	µg.h/mL	area under the concentration versus time curve from time 0 to infinity
$\%AUC_{(tlast-\infty)}$	%	fraction of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	h	time of the maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (for prednisone only)
V_z/F	L	apparent total body clearance of drug calculated after extra-vascular administration (for prednisone only)
CL_{ss}/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (for prednisone only)
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration (for prednisone only)

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
CL/F and Vz/F will be reported for profile day 1, whereas CLss/F and Vss/F will be reported for profile day 30.

If deemed necessary, additional model-based analysis may be performed.

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual plasma PK parameters, except for pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}.

- $AUC_{0-\infty}$ values where the percentage of the total area extrapolated is more than 20% will be flagged. Any $AUC_{0-\infty}$ value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{1/2}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on last predicted quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where 2 or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be C_{min} for the dosing interval.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average concentration for single-dose data will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.
- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated, and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

10.3.2 Pharmacokinetic Statistical Methodology

Dose Proportionality (Part A IV doses only)

The log-transformed PK parameters AUC(0-tlast), AUC(0-∞), and C_{max} will be evaluated for dose proportionality using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric least square (LS) means and corresponding 90% confidence intervals (CIs). The power model will be:

log(parameter) = log(dose) + participant + error.

Example SAS code:

```
proc mixed data = xxx;
   by parameter;
   model log_pk = log_dose / alpha = 0.1 cl solution outpred=resids ddfm = kr2;
   estimate 'xx mg' intercept 1 log_dose yy / alpha = 0.1 cl; /* log value of xx */
   estimate 'zz mg – xx mg' log_dose pp / alpha = 0.1 cl; /* pp = diff in log values of zz and xx*/
   ods output solution = est estimates = estims;
run;
```

10.4 Pharmacodynamic Assessment

10.4.1 Pharmacodynamic Analysis

The following PD parameters will be determined using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or higher):

LY3872386 Part B – MAD

CCI [redacted]

Parameter	Units	Definition
AUC	µg.h/mL	area under the concentration versus time curve
C_{max}	µg/mL	maximum observed concentration
t_{max}	h	time of maximum observed drug concentration

Part C -Multiple doses of Prednisone and Prednisolone:

CCI [redacted]

Parameter	Units	Definition
AUC	µg.h/mL	area under the concentration versus time curve
C_{max}	µg/mL	maximum observed drug concentration

t_{max}	h	time of maximum observed drug concentration

10.4.2 Pharmacodynamic Statistical Methodology

All derived PD concentrations CCI [redacted] will be summarized by part and treatment, and listed. Plots will also be produced.

CCI [redacted]

10.5 Pharmacokinetic/Pharmacodynamic Analyses

PK/PD modeling may be evaluated to characterize the exposure-response relationships between LY3872386 concentrations and various PD endpoints, provided the data are sufficient. This analysis, if performed, will be performed, and reported by Lilly.

10.6 Safety and Tolerability Assessments

10.6.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A TEAE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. All TEAEs will be summarized by part, treatment, severity, and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of TEAEs will be summarized by part, treatment, Medical Dictionary for Regulatory Activities (MedDRA) (version is documented in the Data Management Plan [DMP]) system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any SAEs will be listed by treatment group. For Parts B and C, AEs by day of onset will be presented, where onset time is based on the last dose received.

Discontinuations due to AEs will be listed.

10.6.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (version is documented in the DMP). Concomitant medication will be listed.

10.6.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by part, treatment, and time point, together with changes from baseline where baseline is defined as Day 1 predose. Clinical chemistry, hematology, and urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the calculation of summary statistics, <x and ≤x values will be set to 0.5 × x, whereas >x and ≥x values will be set to 2 × x.

10.6.4 Vital signs

Vital signs data will be summarized by part, treatment and time point together with changes from baseline, where baseline is defined as the Day 1 predose. Figures of mean vital signs and mean changes from baseline will be presented over time by treatment.

Values for individual participants will be listed.

10.6.5 Electrocardiogram (ECG)

For Part A, ECGs will be collected in triplicate at all time points excluding screening and the last scheduled follow-up visit. These ECG data will be presented as below. For Parts B and C, ECGs will be presented if collected in triplicate. Otherwise, ECGs from Parts B and C will not be presented, and any clinically significant findings from ECGs will be reported as an AE.

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QRS duration and heart rate. In addition, QT interval corrected using Fridericia's formula (QTcF) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

The ECG data will be summarized by part, treatment and time point together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 predose. Figures of mean ECG data and mean changes from baseline will be presented by part and treatment. The frequency of participants with a maximum increase from baseline in QTcF interval will be summarized by part, and for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of participants with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

Concentration-QTc Analysis (Part A only)

A plasma LY3872386 concentration-QTc analysis will be performed to assess the relationship between changes from baseline (mean of Day 1 predose assessments) in QTcF (ΔQTcF) and plasma LY3872386 concentrations across all treatments. IV and SC data will be pooled.

A linear mixed effects analysis model will be employed with ΔQTcF as the response variable, time-matched LY3872386 concentration as the explanatory variable (0 for PBO), centered baseline QTcF as an additional covariate, treatment (PBO=0 or LY3872386 =1), PK profile day, time (nominal time postdose), and the interaction between PK profile day and time as fixed effects, and a random intercept and concentration slope per participant. The model[4] will have the form:

$$\Delta ECG_{i,j,k,l} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{i,j,k,l} + \theta_{3,k} DAY_k + \theta_{4,l} HOUR_l + \theta_{5,k,l} DAY_k \times HOUR_l + \theta_6 (ECG_{i,j,k=1,l=0} - \overline{ECG_{k=1,l=0}}) + \varepsilon_{i,j,k,l},$$

where $\Delta ECG_{i,j,k,l}$ is the change from baseline in QTcF parameter for participant i on treatment j (PBO, or LY3872386) on PK profile day k at l hours postdose. θ_0 is the population mean intercept in the absence of a treatment effect, $\eta_{0,i}$ is the random effect associated with the intercept term θ_0, θ_1 is the fixed effect associated with the dichotomous treatment variable TRT_j, θ_2 is the population mean slope of the assumed linear association between concentration and ΔECG, $\eta_{2,i}$ is the random effect associated with the slope θ_2, $C_{i,j,k,l}$ is the concentration for participant i on treatment j on PK profile day k at l hours postdose, $\theta_{3,k}$ is the fixed effect associated with categorical PK profile day k, $\theta_{4,l}$ is the fixed effect associated with categorical hours postdose l, $\theta_{5,k,l}$ is the fixed effect associated with the interaction term between PK profile day and hours postdose, θ_6 is the fixed effect associated with a participant's centered baseline QTcF value, $\overline{ECG_{k=1,l=0}}$ is the overall mean of $ECG_{i,j,k=1,l=0}$ (all participant's baseline QTcF parameter values, which are denoted as being on PK profile day 1 at hour postdose 0), and $\varepsilon_{i,j,k,l}$ is the residual error. It will be assumed the random effects are multivariate Gaussian distributed with mean vector **0** and an unstructured covariance matrix G, whereas the residuals, $\varepsilon_{i,j,k,l}$, are Gaussian distributed with mean 0 and variance r.

If this model fails to converge, the following covariance structures will be tested in order:

- Compound symmetry
- Variance components

The first covariance structure that converges will be used. If the model still fails to converge, the PK profile day-by-hour interaction term, followed by the random effects for slope, followed by intercept, will be removed until convergence is achieved. Other covariance structures may be considered if deemed appropriate.

The centered baseline QTcF will be derived as follows:

- Calculate the arithmetic mean of the triplicate QTcF parameter for each subject at each timepoint and use this in all subsequent calculations below.
- Calculate the overall baseline QTcF value, which is the mean of all participants' baseline QTcF values.
- For each participant, subtract the overall baseline QTcF value from their own individual baseline QTcF value. This will be each participant's centered baseline QTcF.

For postdose concentrations that are below the quantifiable lower limit of the assay (BQL), the following will be applied:

- For the PBO arm, all LY3872386 concentrations will be imputed as 0.
- For the LY3872386 arms, BQL concentrations will be treated as missing without any imputation.

The LY3872386 concentration slope and corresponding 90% CI will be reported. The model will also be used to derive the predicted ΔQTcF and PBO-corrected ΔQTcF (ΔΔQTcF) at the geometric mean C_{max} of each dose level (PBO=0) for the last PK profile day along with the corresponding 90% CIs in a tabular format.

All ΔQTcF versus time matched LY3872386 concentrations will be plotted, with PBO concentration set to zero. A linear regression line from the model above will be included on the plot along with the corresponding 90% CI.

Predicted ΔΔQTcF from the above model versus LY3872386 concentration will also be plotted. The plot will include a linear regression line from the model above, corresponding 90% CI, and reference lines at the geometric mean C_{max} for each dose.

To check the model covariates are adequate, a scatter plot will be produced plotting the residuals of the fitted model versus LY3872386 concentration. A locally estimated scatterplot smoothing curve with 95% CI will be fitted to aid with this assessment.

The hysteresis loop plot between mean ΔΔQTcF and geometric mean LY3872386 concentration will be generated through 24 hours postdose in a temporal order for each PK profile day, with all LY3872386 doses combined. If deemed appropriate, further timepoints may be included if 24 hours does not adequately encapsulate the hysteresis loop. Mean ΔΔQTcF will be derived by performing a 2-sample t-test at each time point independently, with the 2 groups consisting of PBO and the combined LY3872386 treatments.

Similar analysis will be conducted for RR, HR, PR, and QRS.

Examples of the SAS code that will be used are as follows:

```
proc mixed data=xxx alpha=0.1;
  by param;
  class trt(ref='0') time subjid;
  model ΔECG = basec trt day hour day*hour conc / cl alpha=0.1 ddfm=kr2
residual;
  random intercept conc / subject=subjid type=un;
  estimate 'PBO' intercept 1 trt 0 1 conc 0/ cl alpha=0.1;
  estimate 'Δ at XX mg' intercept 1 trt 1 0 conc [cmax] / cl alpha=0.1;
  estimate 'ΔΔ at XX mg' trt 1 -1 conc [cmax] / cl alpha=0.1;
  ods output solutionF=sol;
  ods output estimates=estim;
run;
```

10.6.6 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.8 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Use of acetaminophen during the study, which has potential for hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by part and treatment, if deemed appropriate, and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

10.6.7 Immunogenicity Assessments

Upon full assay validation, treatment-emergent antidrug antibodies (TE ADAs) may be assessed in line with Protocol section 9.3.4.4.

The relationship between the presence of antibodies and PK parameters of LY3872386 may be assessed if deemed appropriate.

10.6.8 Immunological status assessments

The WBC subpopulations (including, but not limited to, total B cells, total T cells, and NK cells), will be evaluated.

These data will be summarized by part, treatment, and time point, and listed. Changes from baseline will also be presented, where baseline is defined as the Day 1 predose assessment.

10.6.9 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the participant's medical history, alternative causes, and symptoms.

These data will be listed.

10.6.14 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

10.6.15 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10.7 Efficacy Assessment (Part B only)

10.7.1 Efficacy analysis

Efficacy analyses will be conducted on the mITT population. The exploratory efficacy analyses will estimate the effect of the treatment on the exploratory endpoints.

Clinician-rated scales:

Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD)
The vIGA-AD measures the investigator's global assessment of the participant's overall severity of their AD, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification.

Eczema Area and Severity Index (EASI)
The EASI assesses 4 clinical signs of disease, each on a 0 to 3 scale: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification. Scores range from 0 to 72. The EASI evaluates 2 dimensions of AD: disease extent and clinical signs. Body surface area affected by AD will be derived from data collected as part of the EASI assessment.

SCORing Atopic Dermatitis (SCORAD)
The SCORAD index assesses: 1) 6 clinical signs of disease, each on a 0 to 3 scale, 2) the extent of involved surface area, up to 100%, and 3) subjective evaluations of itch and sleeplessness, each on a 0 to 10 scale. Scores range from 0 to 103.

Participant-rated scales:

Dermatology Life Quality Index (DLQI)
The DLQI is a 10-item questionnaire that covers 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period for this scale is over the "last week." Response categories include "a little," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and "not at all" or unanswered ("not relevant") responses scored as 0. Scores range from 0 to 30, with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 or 1 is considered to indicate no effect on a participant's health-related quality of life, and a 4-point change from baseline is considered the minimal clinically important difference threshold.

Itch Numeric Rating Scale (NRS)
The Itch Numeric Rating Scale is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall

severity of a patient's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours.

Patient-Oriented Eczema Measure (POEM)

The Patient-Oriented Eczema Measure assesses the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the last week. Response categories include "No days," "1 to 2 days," "3 to 4 days," "5 to 6 days," and "Every day," with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0 to 28, with higher total scores indicating greater disease severity.

10.7.2 Efficacy Statistical Methodology

Descriptive statistics

Analysis of covariance (ANCOVA)

The mean percent change from baseline CCI [redacted] data will be analyzed on Weeks 1 and 12 by an ANCOVA model with baseline as a covariate and treatment as a fixed effect to estimate the LS means and corresponding 90% CIs.

Example SAS code for the ANCOVA:

```
proc mixed data=saf1 method=reml;
  by param1;
  class treatment;
  model change = base treatment / residual cl alpha=0.1 ddfm=kr2;
  lsmeans treatment / alpha=0.1 cl pdiff;
  ods output lsmeans=lsmeans1 diffs=diff;
run;
```

11. INTERIM ANALYSES

No interim statistical analyses are planned.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Brown H, Prescott R. Applied Mixed Models in Medicine. Chichester: John Wiley & Sons, 1999.

4. Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. [Published correction appears in J Pharmacokinet Pharmacodyn. 2018;45(3):399]. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397.

14. DATA PRESENTATION

14.1 Derived Parameters

Individual derived parameters (e.g., PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g., C_{max}, should be reported

as received. Observed time data, e.g., t_{max}, should be reported as received. Number of observations and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

15. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable

Signature Page for VV-CLIN-133144 v1.0

Approval	PPD 31-Oct-2023 12:18:20 GMT+0000

Approval	PPD 31-Oct-2023 17:34:02 GMT+0000

Approval	PPD 31-Oct-2023 19:26:28 GMT+0000

Approval	PPD 31-Oct-2023 21:00:31 GMT+0000

Signature Page for VV-CLIN-133144 v1.0