Statistical Analysis Plan J3V-MC-KKAA V2

# A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3844583 in Healthy Participants, and Multiple-Dose Study of LY3844583 in Healthy Participants and Patients with Atopic Dermatitis

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# STATISTICAL ANALYSIS PLAN

**A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3844583 in Healthy participants, and Multiple-Dose Study of LY3844583 in Healthy Participants and Patients with Atopic Dermatitis**

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## 2. ABBREVIATIONS

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

| | |
|---|---|
| %AUC($t_{last}$-∞) | Percentage of AUC(0-∞) extrapolated |
| ADA | Anti-drug antibody |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AtD | Atopic dermatitis |
| AUC | Area under the concentration versus time curve |
| AUC(0-∞) | Area under the concentration versus time curve from time zero to infinity |
| AUC(0-$t_{last}$) | Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration |
| AUC(0-τ) | area under the concentration versus time curve over a dosing interval |
| BQL | Below the quantifiable lower limit of the assay |
| CI | Confidence interval |
| CL | total body clearance of drug calculated after intravenous administration (Day CCI for Part B and Day CCI for Part C only) |
| CL/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 |
| CV | Coefficient of variation |
| DLQI | Dermatology Life Quality Index |
| DN_AUC(0-∞) | Dose normalized AUC versus time curve from time zero to infinity |
| DN_AUC(0-$t_{last}$) | Dose normalized AUC versus time curve from time zero to t, 't' is last time point with a measurable concentration. |
| DN_$C_{max}$ | Dose normalized maximum observed drug concentration. |
| EASI | Eczema Area and Severity Index |



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| | |
|---|---|
| EC | Early Clinical |
| ECG | Electrocardiogram |
| F | Absolute bioavailability |
| GITR | Glucocorticoid-induced tumor necrosis factor receptor |
| ICH | International Conference on Harmonisation |
| IP | Investigational product |
| ISR | Injection-site reaction |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LLOQ | Lower limit of quantification |
| LS | Least square |
| MAD | Multiple-ascending dose |
| mBOCF | Modified baseline observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRE | Magnetic resonance elastography |
| NRI | Nonresponder imputation |
| NRS | Skin Pain Numeric Rating Scale |
| PD | Pharmacodynamic |
| POEM | Patient- Oriented Eczema Measure |
| PK | Pharmacokinetic |
| PR | Pulse rate |
| QTcF | Fredericia's corrected QT interval |
| $R_A$ | accumulation ratio based upon AUC(0-τ) |
| RO | Receptor occupancy |
| SAD | Single-ascending dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SCORAD | SCORing Atopic Dermatitis |
| SD | Standard deviation |
| $t_{1/2}$ | Half-life associated with the terminal rate constant ($\lambda_z$) in non-compartmental analysis |



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| | |
|---|---|
| TE-ADA | Treatment-emergent antidrug antibody |
| TE-ADA+ | Treatment-emergent antidrug antibody positive |
| TEAE | Treatment-emergent adverse event |
| TFLs | Tables, Figures, and Listings |
| $t_{max}$ | Time of maximum observed drug concentration |
| VAS | Visual analog scale |
| vIGA-AD | Validated Investigator's Global Assessment for Atopic Dermatitis |
| $V_{ss}$ | Apparent volume of distribution at steady state after intravenous administration |
| $V_{ss}/F$ | Apparent volume of distribution at steady state after extravascular administration |
| $V_z$ | Volume of distribution during the terminal phase after intravenous administration |
| $V_z/F$ | Apparent volume of distribution during the terminal phase after extra-vascular administration |
| WBC | White blood cell |
| WHO | World Health Organization |



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## 3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 14 March 2022) and protocol amendments a (dated 23 January 2023), b (dated 09 February 2023), c (dated 12 May 2023) and d (dated 08 June 2023).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK), efficacy 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. 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 Harmonisation (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].



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## 4. STUDY OBJECTIVES, ENDPOINTS AND ESTIMANDS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the safety and tolerability of LY3844583 after single and multiple dose administrations in healthy participants and after repeat-dose administration in the participants with AtD. | • Incidence of AEs, TEAEs, and SAEs |
| **Secondary** | |
| • To characterize the PK of LY3844583 following single- and multiple-dose administrations in healthy participants and after repeat dosing in participants with AtD. | • $C_{max}$ and AUC |
| **Exploratory** | |
| CCI | |




Abbreviations: AE = adverse event; AtD = atopic dermatitis; AUC = area under the concentration versus time curve; $C_{max}$ = maximum observed drug concentration; CCI ; CCI ; PK = pharmacokinetics; SAE = serious adverse event; CCI ; TEAE = treatment-emergent adverse event; CCI ; CCI ; CCI

**Estimands**

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) will be listed and, if the frequency of events allows, descriptive statistics will summarize the safety data per race and ethnicity. Symptoms, their incidence, severity, and association with investigational product (IP), as perceived by the investigator, will be reported separately for each treatment. All TEAEs will be summarized across each part of the study by system organ class and by decreasing frequency according to the Medical Dictionary for Regulatory Activities.

# 5. STUDY DESIGN

## 5.1 Overall Design

Study J3V-MC-KKAA is a first-in-human trial designed to evaluate safety, tolerability, PK and target engagement of LY3844583 in healthy participants and participants with atopic dermatitis (AtD), with additional assessments of clinical PD and efficacy in participants with AtD. The inclusion of healthy Japanese and Chinese participants in this study will facilitate the inclusion of Japanese and Chinese participants in subsequent clinical trials. The study will be conducted in 3 parts as follows:

- Part A (single ascending dose (SAD)) will assess the safety, tolerability, PK, and receptor occupancy (RO) of single subcutaneous (SC) and intravenous (IV) doses of LY3844583 in healthy participants.
- Part B (multiple ascending dose (MAD)) will assess the safety, tolerability, PK, and RO of multiple IV and/or SC doses of LY3844583 in healthy participants.
- Part C (repeat dose) will assess the safety, tolerability, PK, RO, and exploratory data of multiple IV or SC doses of LY3844583 in participants with AtD.

Figure 1 illustrates the study schema and demonstrates the relationship among Parts A, B, and C. Part A will begin first and will inform and thereby trigger the initiation of Parts B and C.



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The study will consist of 3 periods.

**Screening period for SAD Part A, MAD Part B, and repeat-dose Part C**

Screening may occur up to [redacted] days prior to Day [redacted] of the study. After obtaining informed consent, participants will be screened for eligibility.

Participants who are not enrolled within [redacted] 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**

**SAD Part A**

Part A will be a SAD study and will be comprised of 5 cohorts and 2 optional cohorts. Each cohort will consist of approximately [redacted] healthy participants, who will be randomized to receive LY3844583:placebo in a [redacted] manner at each dose level, except Cohort 5, who will be randomized to receive LY3844583:placebo in a [redacted] manner. Optional Cohorts 6 and 7 may be enrolled depending on emerging data from earlier cohorts.

The planned doses are [redacted] mg SC (Cohort 1), [redacted] mg SC (Cohort 2), [redacted] mg SC (Cohort 3), [redacted] mg IV (Cohort 4), and [redacted] mg IV (Cohort 5). Study intervention will be administered as a single dose on Day [redacted] followed by a [redacted]-week follow-up period. Dose escalation will be based on the review of available data from the ongoing cohorts. The dose for optional Cohorts 6 and 7 will be decided based on emerging data from earlier cohorts.

A sentinel dosing strategy will be utilized in Cohorts 1 and 2 to minimize the participant risk. The initial 2 participants in each of these cohorts will be randomized to receive LY3844583:placebo in a [redacted] manner on the same day. With sentinel dosing, only 1 participant will be dosed at a time, and the second participant will not be dosed until the first participant's administration is complete. [redacted] which is similar to reports for antibody therapies (Ryman and Meibohm 2017). Thus, after at least [redacted] days of post sentinel dosing, the remaining participants in the cohort will be dosed based on the available safety and tolerability data.

The participants in the [redacted] mg IV and [redacted] mg IV cohorts will be dosed in sequence, each following, at a minimum, at least approximately 1 hour after the completion of the administration for the prior participant.

Participants will be monitored for safety, including injection-site reactions (ISRs), and samples will be collected. Participants will be discharged from the clinical research unit (CRU) on Day [redacted] after all study assessments have been completed during the treatment period and in agreement with the investigator.



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**MAD Part B**

Part B will be a MAD study in healthy participants and will comprise of 2 cohorts to assess any acute safety/tolerability events associated with a second and/or third exposure.

After the first dose on Day [CCI] participants will undergo clinical assessments, safety monitoring, and samples will be collected. Participants will be discharged from the CRU at the discretion of the investigator. In Cohort 1, participants will receive up to [CC] additional doses on Days [CCI]. In Cohort 2, participants will receive up to [CC] additional doses on Days [CCI] Participants will be required to visit the CRU on an outpatient basis for clinical assessments and sample collection.

The planned doses are [CCI] mg IV [CCI] in Cohort 1 and ≤[CCI] mg IV or SC [CCI] in Cohort 2. The route and frequency will be confirmed based on the emerging data from SAD cohorts. A decision regarding the MAD Cohorts 1 and 2 doses will be taken following review of available data from Part A of the study.

**Repeat-dose Part C**

Part C will be a repeat-dose study in up to [CCI] patients with AtD with [CCI] LY3844583 and [CC] placebo.

The planned dose is ≤[CCI] mg SC or IV. Study intervention will be administered on Day [CC] followed by dose administration [CCI] or [CCI] for [CCI] weeks. The dose will be administered at the discretion of the investigator and in discussion with the sponsor.

**For all study parts**

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.

Participants in all parts of the study should follow local guidance and CRU precautions to minimize risk for infection, including Coronavirus Disease 2019.

**Follow-up period for SAD Part A, MAD Part B, and repeat-dose Part C**

Participants will be required to return to the CRU for clinical assessments and blood samples on an outpatient basis. The final follow-up visit will be approximately [CCI] weeks after single dose in Part A, [CCI] weeks after the last dose of study intervention in Part B, and [CCI] weeks after the last dose of study intervention in Part C.



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## 6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs. These are the planned dose levels/frequencies, if during the conduct of the study the dose levels are changed then the TFLs will reflect the actual dose levels/frequencies.

| Part | Planned Dose / Administration Route | Treatment order in TFL |
|---|---|---|
| A | Placebo SC | 1 |
| | Placebo IV | 2 |
| | CCI mg LY3844583 SC | 3 |
| | CCI mg LY3844583 SC | 4 |
| | CCI mg LY3844583 SC | 5 |
| | CCI mg LY3844583 IV | 6 |
| | CCI mg LY3844583 IV | 7 |
| B | Placebo IV* | 1 |
| | CCI mg LY3844583 IV CCI | 2 |
| | CCI mg LY3844583 IV CCI | 3 |
| C | Placebo IV CCI | 1 |
| | CCI mg LY3844583 IV CCI | 2 |

Abbreviations: IV = intravenous; SAD = single-ascending dose; SC = subcutaneous, CCI

*Footnote to be added to Part B TFLs to specify "Placebo IV was CCI dosing in cohort 1 and CCI dosing in cohort 2".

## 7. BLINDING

This is a randomized participant- and investigator-blind study. 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. All study site personnel, except staff who prepare the study intervention, will 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.

## 8. SAMPLE SIZE JUSTIFICATION

The study will enroll approximately CCI participants (CCI healthy participants and up to CCI patients with AtD). An additional CCI participants in SAD Cohorts 6 and 7 may be enrolled depending on emerging data.



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The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK and is not powered on the basis of any a priori statistical hypothesis testing results. The sample sizes for Parts A and B are not adjusted to account for dropouts. The sample size for Part C is adjusted to account for potential dropouts. However, the protocol allows replacement if it is deemed necessary to obtain sufficient data for interpretation.

For purposes of this study, a participant completes the study when all scheduled procedures shown in the SoA have been finished. Participants who withdraw before completing all dosing administrations may be replaced. Replacement participants will complete the entire study period. Participants who discontinued the study following required dose administration(s) but before completing may be replaced at the discretion of the sponsor and investigator. The replacement participant where possible, should be Japanese, Chinese or non-Japanese and non-Chinese to match the discontinued participant.

# 9. DEFINITION OF ANALYSIS POPULATIONS

The “Enrolled” population will consist of all participants who sign informed consent.

For Part C only, the “Intent-to-treat (ITT)” population will consist of all randomized participants. 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).

For Part C only, the “Modified ITT (mITT)” population will consist of all randomized participants who receive at least 1 dose of study treatment. 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 participations who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

The “PK analysis set” will consist of all randomized participants who receive at least 1 dose of the study drug and have evaluable PK data.

The “Pharmacodynamic” population will consist of all participants who received at least one dose of study drug or placebo and have evaluable PD data.

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

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,

min, max and n; for log-normal data (e.g. the PK parameters: area under the concentration versus time curves (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 will be provided for all participants, separately by population (for example, Japanese and non-Japanese or Chinese and non-Chinese), and separately for healthy participants and patients with AtD, as appropriate. Tests of statistical significance will not be performed due to the small sample size per treatment group. 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.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline 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

A detailed description of participant disposition will be provided at the end of the study, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete the study or discontinue, both overall and by reason for discontinuation for each part and treatment.

Participant demographic characteristics and for Part C medical status at baseline (for example, prior therapies and pre-existing conditions) will be recorded, listed, and summarized overall and by treatment group using descriptive statistics. The demographic variables will include age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index. For Part C, vIGA-AD, EASI, SCORAD, NRS, POEM and DLQI will also be included.

Other participant characteristics may be summarized overall and by treatment group as deemed appropriate.

## 10.3 Pharmacokinetic Assessment

### 10.3.1 Pharmacokinetic Analysis

The PK parameters will be determined using non-compartmental methods applied with a validated software program (WinNonlin Phoenix Version 8.1 or later).

Serum concentrations of LY3844583 will be used to determine the following PK parameters, when possible:

**Part A**

| Parameter | Units | Definition |
|---|---|---|
| AUC(0-∞) | µg*h/mL | area under the concentration versus time curve from time zero to infinity |
| AUC(0-$t_{last}$) | µg*h/mL | area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration |
| %AUC($t_{last}$-∞) | % | percentage of AUC(0-∞) extrapolated |
| $C_{max}$ | µg/mL | maximum observed drug concentration. |
| $t_{max}$ | h | time to reach maximum observed concentration |
| $t_{1/2}$ | h | half-life associated with the terminal rate constant ($\lambda_z$) in non-compartmental analysis |
| CL/F | L/h | apparent total body clearance of drug calculated after extra-vascular administration |
| CL | L/h | total body clearance of drug calculated after intravenous administratio |
| $V_z$/F | L | apparent volume of distribution during the terminal phase after extra-vascular administration |
| $V_{ss}$/F | L | apparent volume of distribution at steady state after extra-vascular administration |
| $V_z$ | L | volume of distribution during the terminal phase after intravenous administration |
| $V_{ss}$ | L | apparent volume of distribution at steady state after intravenous administration |
| DN_AUC(0-∞) | mg/µg*h/mL | dose normalized AUC versus time curve from time zero to infinity |
| DN_AUC(0-$t_{last}$) | mg/µg*h/mL | dose normalized AUC versus time curve from time zero to t, 't' is last time point with a measurable concentration. |
| DN_$C_{max}$ | mg/µg/mL | dose normalized maximum observed drug concentration. |
| F | % | absolute bioavailability |

Absolute bioavailability (F) may be estimated using the geometric mean extent of absorption values based on Cohort 3 (CCI mg IV) and Cohort 4 (CCI mg SC) where the same dose is administered:

$$F = \frac{\text{Dose}_{IV} * \text{Gmean AUC}(0-\infty)_{EV}}{\text{Dose}_{EV} * \text{Gmean AUC}(0-\infty)_{IV}}$$



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**Parts B and C**

| Parameter | Units | Definition |
|---|---|---|
| AUC(0-τ) | µg*h/mL | area under the concentration versus time curve over a dosing interval |
| $C_{max}$ | µg/mL | maximum observed drug concentration (Day CCI for Part B; Day CCI for Part C) |
| $t_{max}$ | h | time of maximum observed drug concentration (Day CCI for Part B; Day CCI for Part C) |
| $t_{1/2}$ | Day | half-life associated with the terminal rate constant ($\lambda_z$) in non-compartmental analysis (Day CCI for Part B and Day CCI for Part C only) |
| CL | L/h | total body clearance of drug calculated after intravenous administration (Day CCI for Part B and Day CCI for Part C only) |
| $V_z$ | L | volume of distribution during the terminal phase after intravenous administration (Day CCI for Part B and Day CCI for Part C only) |
| CL/F | L/h | apparent total body clearance of drug calculated after extra-vascular administration (Day CCI for Part B and Day CCI for Part C only) |
| $V_z$/F | L | apparent volume of distribution during the terminal phase after extra-vascular administration (Day CCI for Part B and Day CCI for Part C only) |
| $R_{A(AUC)}$ | N/A | accumulation ratio based upon AUC(0-τ) (Day CCI for Part B, and Day CCI for Part C only) |
| $R_{A(Cmax)}$ | N/A | accumulation ratio based upon $C_{max}$ (Day CCI for Part B, and Day CCI for Part C only) |

For Part B and C, trough (predose) serum concentrations of LY3844583 will be listed and summarized. For Part B, $C_{max}$, $t_{max}$, and AUC(0-τ) will be calculated and summarized for first dose on Day CCI and last dose on Day CCI For Part C, $C_{max}$, $t_{max}$ and AUC(0-τ) will be calculated and summarized for first dose on Day CCI and last dose on Day CCI

PK parameters will be summarized by cohort, and may also be summarized by cohort and ethnicity. Subgroup comparisons of Japanese versus non-Japanese participants as well as Chinese versus non-Chinese participants may be performed using graphical and tabular comparisons. If to summarize by cohort and ethnicity, the following comparison may be carried out:

- SAD Part A Cohort 4 Japanese vs non-Japanese/non-Chinese participants;
- SAD Part A Cohort 5 Japanese vs Chinese vs non-Japanese/non-Chinese participants
- MAD Part B Cohort 2 Chinese vs non-Japanese/non-Chinese participants.
- Optional SAD Part A Cohorts 6 and 7, if enrolled and depending on the participant's ethnicity, Japanese vs non-Japanese/non-Chinese participants.

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.



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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 PK parameters, except for non-bolus pre-dose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- $C_{max}$ 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 serum concentrations above the LLOQ, with at least one of these concentrations following $C_{max}$.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) 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 serum 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 $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ 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 predicted $C_{last}$ 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). Serum concentrations reported as BQL will be set to a value of zero when all of 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 two 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 Parts B and C multiple-dosing data, where the pre-dose concentration is missing, the value to be substituted will be $C_{min}$ for the dosing interval [this is the default WinNonlin method].

**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 from non-endogenous compounds 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



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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 pharmacokinetic 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 pharmacokinetic profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For pharmacokinetic 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

All of the PK parameters will be summarized and listed by cohort using descriptive statistics. Individual concentration versus time profiles and average concentration versus time profiles will additionally be presented. For Part B and C, descriptive statistics will be performed on the trough concentrations. $C_{max}$ , $t_{max}$ , and AUC(0-τ) values will also be summarized for Part B and C (Day [redacted] and Day [redacted] for Part B; Day [redacted] and Day [redacted] for Part C).

The LY3844583 PK parameters will be analyzed to estimate PK dose proportionality for Part A. Log-transformed AUC (0-$t_{last}$), AUC (0-∞) and $C_{max}$ parameters will be evaluated using a power model with ethnicity as a covariate across the SC and IV dose ranges separately to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals (CIs). The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach. The analysis model will also be used to estimate between-participant variability.

Example of the SAS code for the power model analysis:

```
proc mixed data=xxx;
class ethnicity;
model log_pk = log_dose ethnicity / alpha=0.1 cl solution outpred=resids
ddfm=kr;
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; /*Difference in log
values of zz and xx*/
ods output solutionf=est;
ods output estimates=estims;
run;
```

An evaluation of F with consideration of ethnicity or other demographic differences between groups, if considered appropriate, will be performed using SAD Cohorts 3 and 4 data where the same dose is administered both IV and SC. The model will include the log-transformed PK parameter AUC (0-∞) as the dependent variable, ethnicity (and any other relevant demographic variables) as a covariate and treatment as a fixed effect.

Subgroup comparisons of Japanese versus non-Japanese participants as well as Chinese versus non-Chinese participants may be performed using graphical and tabular comparisons. If to summarize by cohort and ethnicity, the following comparison may be carried out

- SAD Part A Cohort 4 Japanese vs non-Japanese/non-Chinese participants;
- SAD Part A Cohort 5 Japanese vs Chinese vs non-Japanese/non-Chinese participants



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- MAD Part B Cohort 2 Chinese vs non-Japanese/non-Chinese participants.
- Optional SAD Part A Cohorts 6 and 7, if enrolled and depending on the participant's ethnicity, Japanese vs non-Japanese/non-Chinese participants

To facilitate the planning for future clinical studies, additional analyses may be conducted as appropriate. The concentration-time data may be analyzed using a nonlinear mixed effects model. If required, this analysis will be performed by Lilly rather than Fortrea.

## 10.4 Pharmacodynamic Assessment

### 10.4.1 Pharmacodynamic Analysis

Receptor occupancy, WBC subpopulations, (including T-cell subpopulations), and immunoglobulin concentrations will be explored. The measures of concentrations will be graphically evaluated across dose levels and explored as a surrogate for target engagement and/or mechanism of action by plotting mean profiles by part and treatment. Data will be listed and summarized by part, timepoint and treatment along with changes from baseline.

Model-based analyses to utilize the data to estimate RO, relationships with PK, and/or safety may also be performed if appropriate. Exploratory analyses of CCI [redacted] may be conducted. If required, this model-based analysis will be performed by Lilly rather than Fortrea.

### 10.4.2 Skin Biopsies

In part C only, biomarkers of disease from skin biopsies will be listed.

## 10.5 Safety and Tolerability Assessments

### 10.5.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (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 treatment-emergent AE 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. Treatment-emergent AEs 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 treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 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 serious AEs will be listed and the frequency of serious AEs by treatment will also be presented. AEs by week of onset will be presented for multiple dosing. If the frequency of events allows, data will be summarized by race and ethnicity.



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Discontinuations due to AEs will be listed.

### 10.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version Mar 2022 B3). Concomitant medication will be listed.

Rescue medication will be listed and includes but is not limited to the below. A review will be conducted prior to the database lock to identify any other rescue medications administered.

- Triamcinolone 0.1% cream
- Hydrocortisone 2.5% cream
- Tacrolimus 0.03%
- Tacrolimus 0.1%
- Pimecrolimus 1%
- Crisaborole

### 10.5.3 Clinical laboratory parameters

All clinical chemistry and hematology data and their changes from baseline will be summarized by part, parameter and treatment, and listed. 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. Where applicable, data will be summarized by race/ethnicity and overall.

### 10.5.4 Vital signs

Vital signs data will be summarized by part and treatment together with changes from baseline, where baseline is defined as as the last evaluable value before the first dose. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment. Where applicable, data will be summarized by race/ethnicity and overall.

Values for individual participants will be listed.

### 10.5.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the pulse rate (PR), QT, QT interval corrected using Bazett's formula (QTcB) intervals, 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 timepoint together with changes from baseline, where baseline is defined as the as the last evaluable value before the first dose (mean of triplicate). Figures of mean ECG data and mean changes from baseline will be presented by

part. The frequency of participants with a maximum increase from baseline in QTcF interval will be summarized 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. Where applicable, data will be summarized by race/ethnicity and overall.

**Serum PK Concentration versus Delta and Double Delta ECG Parameter Analysis**

For all cohorts, a serum LY3844583 concentration-ECG parameter analysis will be performed to assess the relationship between placebo-corrected (double delta) changes from baseline in QTcF and serum LY3844583 concentrations across all treatments in each Part. Further details on how these will be calculated:

- Calculate the baseline ECG value for each participant.
- Calculate the change from baseline of the mean triplicate at each post-baseline time point for each individual participant.
- Calculate the mean ECG parameter value across all participants at baseline.
- For each participant, subtract the overall baseline ECG parameter value across all participant from their own individual baseline ECG parameter value. This will be each participant's centered baseline ECG parameter value.
- Predose below the quantifiable lower limit of the assay (BQL) LY3844583 concentration data will be set to 0.
- Postbaseline BQL concentration data will be imputed as follows:
    - For the placebo arm, all PK concentrations will be imputed as 0.
    - For the LY3844583 arm, BQL concentrations will be treated as missing without any imputation and excluded from the analysis.

The relationship between time-matched LY3844583 concentrations and ECG parameters will be explored graphically by plotting:

- Delta ECG, which is defined as the change from baseline of the ECG parameter value, against LY3844583 concentrations at the same time point and,
- Double delta ECG, which is defined as the placebo-corrected change from baseline of the ECG parameter value, against LY3844583 concentrations at the same time point.

A linear mixed effects analysis model will be employed with delta ECG as the response variable, LY3844583 concentration and centered baseline ECG parameter value as continuous covariates, treatment (Placebo, or LY3844583) and time (in hours) as categorical factors, and a random intercept and slope per patient. Treatment will be coded as a binary variable (Placebo=0 or LY3844583 =1). The model will have the form

$$\Delta ECG_{i,j,k} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{i,j,k} + \theta_{3,k} TIME_k + \theta_4 (ECG_{i,j,k=0} - \overline{ECG_{k=0}}) + \varepsilon_{i,j,k},$$

where $\Delta ECG_{i,j,k}$ is the change from baseline in ECG parameter for patient $i$ on treatment $j$ at time $k$, $\theta_0$ is the population mean intercept in the absence of treatment effect, $\eta_{0,i}$ is the random effect associated with the intercept term $\theta_0$, $\theta_1$ is the fixed effect categorical variable associated with taking LY3844583, $\theta_2$ is the population mean slope of the assumed linear association between concentration and $\Delta ECG_{i,j,k}$, $\eta_{2,i}$ is the random effect of patient $i$ associated with the slope $\theta_2$, $C_{i,j,k}$ is the concentration for patient $i$ on treatment $j$ at time $k$, $\theta_{3,k}$ is the fixed effect associated with time $k$, $TIME_k$ is the nominal time fitted as a categorical factor, $\theta_4$ is the fixed effect associated with the centered baseline ECG, $\overline{ECG_{k=0}}$ is the overall mean of $ECG_{i,j,k=0}$ (the mean of all the baseline ECG parameter values), and $\varepsilon_{i,j,k}$ 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, $\varepsilon_{i,j,k}$, are Gaussian distributed with mean 0 and variance $r$.

If the model fails to converge, different covariance structures may be explored such as vc. If the model still fails to converge, the random effects may be removed, with the slope random effect removed before the random intercept. Model parameters are estimated using maximum likelihood, or restricted maximum likelihood approaches.

The estimated mean change from baseline and placebo-corrected change from baseline in ECG parameter (ΔECG and ΔΔECG respectively) at the observed geometric mean $C_{max}$ of each treatment and two-sided 90% CI at different dose levels will be calculated. The treatment effect of LY3844583, and a 90% CI will also be reported. Residual plots will be produced to assess the adequacy of the model. The hysteresis loop plot between QTcF change from baseline and PK concentration will be generated within 24 hours.

Example of SAS code as follows:

```
proc mixed data=xxx;
by param;
class treat time subjid;
model ΔECG = treat time baseline_ECG PKconc / solution cl
alpha=0.1 ddfm=kr;
random intercept PKconc / type=un subject=subjid solution;
estimate 'Placebo ' intercept 1 treat 1 0 PKconc 0/ CL alpha=0.1;
estimate 'YY mg LY3844583 ' intercept 1 treat 0 1 PKconc [cmax
YYmg] / CL alpha=0.1;
estimate 'YY mg LY3844583 - Placebo' treat -1 1 PKconc [cmax
YYmg] / CL alpha=0.1;
ods output covparms=covp(where=(covparm="Residual"));
ods output solutionF=sol;
ods output estimates=estim;
run;
```

### 10.5.6 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 10.6.1 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 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.

### 10.5.7 Immunogenicity Assessments

The frequency and percentage of participants with pre-existing ADA and with treatment-emergent antidrug antibody (TE-ADA)+ to LY3844583 will be tabulated by treatment. TE-ADAs are defined as those with a titer CCI (CCI ) greater than the minimum required dilution if no ADAs were detected at the baseline (treatment-induced ADA) or those with a CCI (CCI ) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For participants with treatment-emergent antidrug antibody positive (TE-ADA+), the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated in participants with TE-ADA+ if assessed. Where applicable, data will be summarized by race/ethnicity and overall.

The relationship between the presence of antibodies to LY3844583, the PK parameters, LY3844583 concentration, and RO response, including safety and biomarkers, may be assessed if deemed appropriate.

### 10.5.8 Visual Analog Scale Pain Scores

Intensity of pain data will be quantified using a 100-mm validated visual analog scale (VAS). The data will be listed and summarized by part, treatment and time point. Where applicable, data will be summarized by race/ethnicity and overall.

### 10.5.9 Hypersensitivity reactions

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

These data will be listed.



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### 10.5.10 Infusion Site Reactions

The frequency and percentage of participants with a treatment-emergent infusion-site reaction will be summarized by part, treatment and maximum severity. Where applicable, data will be summarized by race/ethnicity and overall.

### 10.5.11 Injection-Site Reactions

The frequency and percentage of participants with a treatment-emergent Injection-site reaction (erythema, induration, categorical pain, pruritus, and edema) will be listed and summarized by part, treatment and maximum severity. Bleeding assessment data will be listed.

Where applicable, data will be summarized by race/ethnicity and overall.

### 10.5.12 Other assessments

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

### 10.5.13 Safety and Tolerability Statistical Methodology

Model-based analyses to utilize the data to estimate RO, relationships with PK, and/or safety may be performed if appropriate. Exploratory analyses of CCI [redacted] may be conducted. If required this analysis will be performed by Lilly rather than Fortrea.

## 10.6 Efficacy Assessments (Part C only)

Efficacy analyses will be conducted on the mITT population. The primary estimand is a composite response in which participants with the intercurrent events of discontinuation or use of prohibited therapies are considered nonresponders. Due to the small sample size, statistical hypothesis tests will not be performed for any efficacy analysis. Instead, efficacy outcomes will be summarized with descriptive statistics. Binary efficacy outcomes will be summarized with the frequency and percent of responders in each treatment group by timepoint. Continuous efficacy outcomes will be summarized with the mean, standard deviation, minimum, and maximum in each treatment group by timepoint. The missing data imputation methods described here will provide a conservative approach for assessing efficacy endpoints when participants permanently discontinue from the study drug or otherwise have missing efficacy data.

Participants who have a disposition status of "STUDY TERMINATED BY SPONSOR" will be excluded from efficacy analyses for visits occurring after the study was terminated.

- Nonresponder imputation (NRI): The NRI method will impute missing data for the analysis of categorical efficacy outcome variables. Participants will be considered nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria, initiate rescue medication, discontinue the study drug for any reason other than study terminated by sponsor, or otherwise have missing clinical efficacy data at the time point of interest.



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- Modified baseline observation carried forward (mBOCF): The mBOCF method will impute missing data for the analysis of continuous efficacy outcome variables. Participants who initiate rescue medication, discontinue the study drug for any reason other than study terminated by sponsor, or otherwise have missing clinical efficacy data will have their baseline observation carried forward to the corresponding endpoint for evaluation.

Additional missing data imputation methods may be used.

Description and Derivation of Primary, Secondary and Exploratory Efficacy Outcomes

| Measure | Description | Variable | Derivation / Comment |
|---|---|---|---|
| Validated Investigator's Global Assessment for AD (IGA) | The validated Investigator's global assessment of the patient's overall severity of their AD, based on a static, numeric 5-point scale from 0 (clear) to 4 (severe). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification. | IGA score | Single item. Range: 0 to 4<br>0 represents "clear"<br>4 represents "severe" |
| | | Change from baseline in IGA score | Change from baseline: observed IGA score – baseline IGA score |
| | | ▪ IGA [0,1] with ≥2-point improvement | ▪ Observed score of 0 or 1 and change from baseline ≤-2 |



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|---|---|---|---|
| Eczema Area and Severity Index (EASI) | The EASI assesses objective physician estimates of 2 dimensions of atopic dermatitis – disease extent and clinical signs by scoring the extent of disease (percentage of skin affected: 0 = 0%; 1 = 1-9%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; 6 = 90-100%) and the severity of 4 clinical signs (erythema, edema/papulation, excoriation, and lichenification) each on a scale of 0 to 3 (0 = none, absent; 1 = mild; 2 = moderate; 3 = severe) at 4 body sites (head and neck, trunk, upper limbs, and lower limbs). Half scores are allowed between severities 1, 2 and 3. Each body site will have a score that ranges from 0 to 72, and the final EASI score will be obtained by weight-averaging these 4 scores. Hence, the final EASI score will range from 0 to 72 for each time point. | EASI score | Derive EASI region score for each of head and neck, trunk, upper limbs, and lower limbs as follows:<br>$EASI_{region}$ = (Erythema + edema/papulation + Excoriation + Lichenification) *(value from percentage involvement), where erythema, edema/papulation, excoriation, and lichenification are evaluated on a scale of 0 to 3 and value from percentage involvement is on a scale of 0 to 6.<br>Then total EASI score is as follows:<br>EASI = 0.1*$EASI_{head\ and\ neck}$ + 0.3*$EASI_{trunk}$ + 0.2*$EASI_{upper\ limbs}$ + 0.4*$EASI_{lower\ limbs}$ |
| | | ▪ Change from baseline in EASI score<br>▪ Percent change from baseline EASI score | Change from baseline: observed EASI score – baseline EASI score<br>% change from baseline:<br>$100 \times \frac{Observed\ score - Baseline}{Baseline}$ |
| | | EASI50 | % Improvement in EASI score from baseline ≥ 50%:<br>% change from baseline ≤ -50 |
| | | EASI75 | % Improvement in EASI score from baseline ≥75%:<br>% change from baseline ≤-75 |
| | | EASI90 | % Improvement in EASI score from baseline ≥90%:<br>% change from baseline ≤-90 |
| SCORing Atopic Dermatitis (SCORAD) | The SCORing Atopic Dermatitis (SCORAD) index uses the rule of nines to assess disease extent (head and neck 9%; upper limbs 9% each; lower limbs 18% each; anterior trunk 18%; back 18%; and genitals 1%). It evaluates 6 clinical characteristics to determine disease severity: (1) erythema,<br>(2) edema/papulation,<br>(3) oozing/crusts, (4) excoriation, (5) lichenification, and (6) dryness on a scale of 0 to 3 (0=absence, 1=mild, | SCORAD score | SCORAD = A/5 + 7B/2 + C, where<br>A is extent of disease, range 0-100<br>B is disease severity, range 0-18<br>C is subjective symptoms, range 0-20 |
| | | ▪ Change from baseline in SCORAD score<br>▪ Percent change from baseline in SCORAD score | Change from baseline: observed SCORAD score – baseline SCORAD score<br>% change from baseline:<br>$100 \times \frac{Observed\ score - Baseline}{Baseline}$ |
| | | SCORAD50 | % Improvement in SCORAD from baseline ≥50%:<br>% change from baseline ≤-50 |



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| | 2=moderate, 3=severe). The SCORAD index also assesses subjective symptoms of pruritus and sleep loss in the last 72 hours on visual analogue scales (VAS) of 0 to 10 where 0 is no itch or sleep loss and 10 is worst imaginable itch or sleep loss. These 3 aspects: extent of disease, disease severity, and subjective symptoms combine to give a maximum possible score of 103. | SCORAD75 | % Improvement in SCORAD from baseline ≥75%:<br>% change from baseline ≤-75 |
| | | SCORAD90 | % Improvement in SCORAD from baseline ≥90%:<br>% change from baseline ≤-90 |

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| Skin Pain Numeric Rating Scale (NRS) | Skin Pain NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours | Skin Pain NRS score | Single item; range 0 to 10. |
| | | ▪ Change from baseline in Itch NRS<br>▪ Percent change from baseline in Itch NRS | Change from baseline: observed Itch score – baseline Itch score<br><br>% change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$ |
| | | 4-point Itch improvement in subgroup of patients with baseline Itch NRS ≥4 | Among participants with baseline ≥4: Change from baseline ≤-4 |
| Patient- Oriented Eczema Measure (POEM) | The POEM is a simple, 7-item, patient-administered scale that assesses disease severity in children and adults. Patients respond to questions about 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," "1-2 days," "3-4 days," "5-6 days," and "Every day" with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0-28 with higher total scores indicating greater disease severity. | POEM score | POEM total score: sum of questions 1 to 7, Range 0 to 28. |
| | | Change from baseline in POEM score | Change from baseline: observed POEM score – baseline POEM score |
| | | 4-point improvement in POEM score in subgroup of patients with baseline ≥4 | Among participants with baseline ≥4: Change from baseline ≤-4 |



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| Dermatology Life Quality Index (DLQI) | The Dermatology Life Quality Index (DLQI) is a simple, patient-administered, 10-item, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of 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 0-30 with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related QoL, and a 4-point change from baseline is considered as the minimal clinically important difference threshold. | Symptoms and feelings domain | Sum of questions 1 and 2, range 0 to 6. |
| | | Daily activities domain | Sum of questions 3 and 4, range 0 to 6. |
| | | Leisure domain | Sum of questions 5 and 6, range 0 to 6. |
| | | Work and school domain | Sum of questions 7 and 7B (if it is answered), range 0 to 3.<br>Responses of "yes" and "no" on Question 7 are given scores of 3 and 0 respectively. If Question 7 is answered "no" then Question 7b is answered with "a lot", "a little", "not at all" getting scores of 2, 1, 0 respectively. |
| | | Personal relationships domain | Sum of questions 8 and 9, range 0 to 6. |
| | | Treatment domain | Question 10, range 0 to 3. |
| | | DLQI total score | DLQI total score: sum of all six DLQI domain scores, range 0 to 30. |
| | | Change from baseline in DLQI | Change from baseline: observed DLQI score – baseline DLQI score |
| | | 4-point improvement in DLQI total score in subgroup of patients with baseline ≥4 | Among participants with baseline ≥4: Change from baseline ≤-4 |
| | | DLQI (0,1) | A DLQI (0,1) response is defined as a post-baseline DLQI total score of 0 or 1 |

The exploratory efficacy analyses will estimate the effect of LY3844583 on the primary and secondary outcomes from baseline to Week [redacted] through Week [redacted]

- [redacted]



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Additional analyses may be performed.

## 11. INTERIM ANALYSES

No interim statistical analyses are planned.

## 12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Participants who have a disposition status of "STUDY TERMINATED BY SPONSOR" will be excluded from efficacy analyses for visits occurring after the study was terminated.

## 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.

## 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. N 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."



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# 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. |
| Final Version 2.0 | 21FEB2024 | To document that participants who have a disposition status of "STUDY TERMINATED BY SPONSOR" will be excluded from the efficacy analysis for visits occurring after the study was terminated.<br><br>To update to reflect protocol amendments a to d. |

NA = not applicable



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Signature Page for VV-CLIN-146615 v1.0

| | |
|---|---|
| Approval | PPD<br>Statistician<br>21-Feb-2024 13:47:31 GMT+0000 |
| Approval | PPD<br>PKPDPMx<br>21-Feb-2024 13:52:19 GMT+0000 |
| Approval | PPD<br>PKPDPMx<br>22-Feb-2024 09:29:50 GMT+0000 |
| Approval | PPD<br>Statistician<br>26-Feb-2024 12:55:50 GMT+0000 |

Signature Page for VV-CLIN-146615 v1.0