Statistical Analysis Plan J4E-MC-IMMB (Version 1)

A Master Protocol for Randomized, Controlled, Phase 2 Clinical Trials of Multiple Interventions for the Treatment of Adults with Moderate-to-Severe Atopic Dermatitis

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Title Page

Protocol Title: A Master Protocol for Randomized, Controlled, Phase 2 Clinical Trials of Multiple Interventions for the Treatment of Adults with Moderate-to-Severe Atopic Dermatitis

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Table of Contents

Table of Contents

Version History

This Statistical Analysis Plan for Study J4E-MC-IMMB is based on the protocol dated 13MAR2023.

Table 1.1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See date on Page 1	Not Applicable	Original version

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe and specify the analyses relevant across the different intervention specific appendices (ISAs) of the atopic dermatitis master protocol (ADMP). The ADMP-specific SAP (MP-SAP) will specify

1. baseline characteristics of interest
2. safety analyses common across ISAs
    a. overall safety including the posttreatment follow-up period, which accounts for safety events after dosing stops but drug has not washed out, and
    b. safety during the induction treatment period, which is common to all ISAs, and
3. analysis framework for borrowing placebo data in the ADMP.

There are no changes to the analyses described in Protocol J4E-MC-IMMB (IMMB).

1.1. Objectives, Endpoints, and Estimands

The clinical research objectives, endpoints, and The clinical research objectives, endpoints, and estimands for specific investigations are detailed in the relevant ISA.

1.2. Study Design

The overall design includes 2 components which, used together, constitute the complete protocol for study conduct: the ADMP is a multinational, multicenter, randomized, double-blind, controlled, platform-type master protocol with ISAs to investigate multiple interventions for atopic dermatitis (AD) at the same time or serially over time. ISAs can begin independently of one another as interventions become available for clinical testing. The ISAs can also finish independently of one another, ending, for example, when the ISA has reached its full planned duration or when interim analyses show that an intervention's criteria for futility or success has been met.

Overall, the design includes 2 components which, used together, constitute the complete protocol for study conduct:

- Master Protocol IMMB explains the platform and contains protocol elements common to every investigation in the platform. Common elements include, but are not limited to, the master protocol screening period and master protocol entry criteria; safety monitoring activities and criteria for discontinuation applicable to every ISA; and statistical analysis methods applicable to every ISA.
- The ISAs provide information on the interventions to be studied, for example, intervention-specific screening activities, background information, benefit/risk, and dose justification; intervention-specific study objectives, endpoints, and estimands; and intervention-specific outcome measurements and statistical analysis methods.

2. Statistical Hypotheses

The master protocol provides a framework for evaluating the safety and efficacy of investigational interventions for AD. The ISAs and ISA-SAPs will provide the specific details on the clinical objectives, endpoints, and efficacy estimands of interest.

2.1. Multiplicity Adjustment

Multiplicity adjustment will generally not be performed for ISAs; refer to Section 2.1 of the ISA-SAP for specific details.

3. Analysis Sets

The populations in Table 3.1 are defined for this study. Depending on the ISA, the modified intent to treat (mITT) and/or safety population may distinguish between induction and maintenance periods. For example, a safety population for the induction period and, separately, a safety population for the maintenance period.

Table 3.1. The Minimum Analysis Sets for the ADMP

Participant Analysis Set	Description
mITT	All randomized participants receiving at least 1 dose of study intervention. Participants will be included in the analysis set according to their randomly assigned intervention.
Safety	All randomized participants receiving at least 1 dose of study interventions. Participants will be included in the analysis set according to the intervention they actually received.

Abbreviations: ADMP = atopic dermatitis master protocol; mITT = modified intent to treat.

4. Statistical Analyses

The MP-SAP will specify analyses and methods for

- patient disposition information
- baseline demographic and disease severity information

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- safety analyses applicable across all ISAs.

The ISA-SAP will specify efficacy estimands and corresponding methodology, and other safety analyses.

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Unless otherwise indicated in the ISA-SAP, the following general considerations are used:

- continuous data will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum
- categorical data will be summarized as frequency counts and percentages
- primary and secondary endpoint analyses will be tested at a 2-sided α level of .05
- baseline values for efficacy analyses will be defined as the last available value before the first dose of study intervention, and
- efficacy and patient-reported outcome analysis models may contain independent variables. These variables may include, but are not limited to, treatment group, baseline disease activity, and geographic region. The ISA-SAP will specify the relevant independent variables.

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4.2. Participant Dispositions

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized among screened participants, and number and percentage of participants who complete the study or discontinue among randomized participants. The reasons for discontinuation will be summarized for each ISA. A summary of important protocol deviations will be provided for each ISA.

Depending on the ISA, participant disposition may be described for both the induction and maintenance treatment periods. The ISA and/or ISA-SAP (Section 4.2) will provide details on additional relevant information for participant disposition.

4.3. Primary Endpoint/Estimand Analysis

Please see Section 4.3 of the relevant ISA-SAP.

4.4. Secondary Endpoints/Estimands Analysis

The MP-SAP will focus on two safety analyses: (1) overall safety profile across treatment periods including posttreatment follow-up, and (2) safety profile during induction. The ISA-SAP will define the treatment groups, if relevant, for the overall and induction safety analyses.

Please see Section 4.4 of the relevant ISA-SAP for secondary endpoints and/or estimands for efficacy analyses or ISA-specific safety analyses.

Estimand for overall safety analyses

A secondary clinical question of interest is: what is the difference between active study intervention versus placebo in the number, percent, and/or incidence rates (IRs) of treatment-emergent adverse events (TEAEs) of interest?

The estimand is described by the following attributes:

- Population: participants with moderate-to-severe AD
- Endpoint(s): number, percent, and/or IRs for first TEAEs of interest
- How to account for intercurrent events:
    - Early Permanent Discontinuation of Study Intervention: TEAEs during the posttreatment follow-up will be considered attributable to the study intervention
    - Use of Prohibited or Rescue Medication: TEAEs after the use of prohibited or rescue medication will be considered attributable to the study intervention.

  - Assignment to Escape Arm (if applicable): if a participant escapes from placebo to active study intervention, subsequent TEAEs will be attributable to the active study intervention, and
  - Assignment to Placebo Withdrawal Arm (if applicable): if a participant is re-randomized from active study intervention to placebo, TEAEs will be considered attributable to the active study intervention until the completion of the study

- Population-level summary: the difference in IRs for TEAEs of interest between participants receiving (rather than assigned to) active study intervention versus placebo, and
- Rationale for estimand:
  - TEAEs of interest for participants receiving active study intervention are considered attributable to study intervention

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  - the use of prohibited or rescue medication are potential components of treatment regimens and should therefore be attributable to study intervention.

Secondary estimand for safety during induction period

A secondary clinical question of interest is: what is the difference between the active study intervention versus placebo (or active comparator) in the number, percent, and/or IRs of TEAEs of interest during the induction treatment period?

The estimand is described by the following attributes:

- Population: participants with moderate-to-severe AD
- Endpoint: number, percent, and/or IRs for first TEAE of interest
- How to account for intercurrent events:
  - Early Permanent Discontinuation of Study Intervention: TEAEs during the posttreatment follow-up visits will not be considered attributable to the study intervention, and
  - Use of Prohibited or Rescue Medication: TEAEs after the use of prohibited or rescue medication, regardless of relation to AD, will be considered attributable to the study intervention
- Population-level summary: the difference in IRs for TEAEs of interest between participants receiving (rather than assigned to) active study intervention versus placebo, and
- Rationale for estimand: TEAEs during the induction period provide the most direct and clean comparison of safety across ISAs because the ADMP requires each ISA to have an induction treatment period. The posttreatment follow-up period is not included due to potentially notable differences across ISAs including, for example, maintenance treatment periods.

4.5. Exploratory Endpoints/Estimands Analysis

The MP-SAP will describe the general principals and process for sharing placebo data from historical studies (either completed ISAs in the ADMP or other AD studies with participant-level data). For all other exploratory analyses, please see Section 4.5 of the relevant ISA-SAP.

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4.6. Safety Analyses

For safety analyses, p-values will not be included unless specified in the ISA-SAP.

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Table 4.1. Baseline and Postbaseline Period Definitions for Overall and Induction Safety Analyses

Analysis Type	Baseline Period	Postbaseline Period
TEAEs (induction safety analyses)	Starts from informed consent date for IMMB to just prior to the time of first dose.	Starts at the time of first dose of the study intervention and ends at the earliest of the following: • Time of discontinuation from ISA • Time of discontinuation from study drug • Time of completing induction treatment period (time of the first dose in the maintenance treatment period, if relevant, or the date of the last visit in the induction treatment period), or • Database cut-off date for ongoing studies
TEAEs (overall safety analyses)	*Randomized in the initial period:* Starts from informed consent date for IMMB to just prior to the time of first dose. *Assigned to Escape Arm from Placebo (if applicable):* From the informed consent date for IMMB to just prior to the time of first dose of active study intervention on the escape arm.	*For participants randomized to active study intervention in the initial period or assigned to escape arm from placebo:* Starts at the time of first dose of the active study intervention and ends at the earliest of the following: • Time of discontinuation from ISA • Time of ISA completion, or • Database cut-off date for ongoing studies *For participants initially randomized to placebo:* Starts at the time of first dose and ends at the earliest of the following: • Time of discontinuation from ISA • Time of ISA completion • Time of first dose on the escape arm (if applicable), or • Database cut-off date for ongoing studies

Analysis Type	Baseline Period	Postbaseline Period
Laboratory tests and vitals (overall safety analyses)	*Randomized in the initial period:* The last available value prior to the first dose of study drug. *Assigned to Escape Arm from Placebo (if applicable):* The last available value prior to the first dose of active study intervention on the escape arm.	*For participants randomized to active study intervention in the initial period or assigned to escape arm from placebo:* Starts at the time of first dose of the active study intervention and ends at the earliest of the following: • Time of discontinuation from ISA • Time of ISA completion, or • Database cut-off date for ongoing studies. *For participants initially randomized to placebo:* Starts at the time of first dose and ends at the earliest of the following: • Time of discontinuation from ISA • Time of ISA completion • Time of first dose on the escape arm (if applicable), or • Database cut-off date for ongoing studies.

Abbreviations: ISA = intervention specific appendix; TEAE = treatment-emergent adverse event.

4.6.1. Extent of Exposure

Please refer to Section 4.6.1 of the ISA-SAP for the extent of exposure analysis.

4.6.2. Adverse Events

Adverse events (AEs) are recorded in the electronic case report form (eCRF). Each AE will be coded to System Organ Classes (SOC) and Preferred Terms (PT), using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of the database lock. Severity of AEs is recorded as mild, moderate, or severe.

TEAEs are defined as events that either first occurred or worsened in severity during the postbaseline period defined in Table 4.1. The MedDRA Lowest Level Terms will be used in defining which events are treatment-emergent (TE). The maximum severity for each Lowest Level Term during the baseline period will be used as baseline. TE status in the presence of incomplete data will be determined through the following rules:

- if an AE has missing severity during the baseline period, then the baseline severity will be considered mild for determining TE status
- AEs with missing severity during the postbaseline period will be considered TE regardless of severity during the baseline period, and
- AEs with insufficient data on start date to determine the relevant period (for example, AE start year is the same as the treatment start year, but the AE start month and day are missing) will be considered TE.

For AEs occurring on the first day of the postbaseline period, the day and time of the AE start date will be compared with the dosing day and time. If such a comparison cannot be made due to incomplete day and time information, the AE will be considered TE.

Summaries of TEAE data will at a minimum include

- the number of participants in the safety population of interest
- the number of participants experiencing the event in the safety population of interest, and
- frequency, or percentage, relative to the safety population of interest.

As noted in Table 4.2, some TEAE analyses will also include:

- person-years at-risk during the postbaseline period (years from start of postbaseline period to the first event of interest or the end of the postbaseline period, whichever is first), and
- (exposure-adjusted) IRs and corresponding confidence intervals.

For events that are sex specific, the denominator, computation of percentage, and IR will only include participants of the given sex.

System Organ Class mapping

MedDRA PTs are assigned to a SOC through primary mappings (defined by MedDRA). Thus, MedDRA PTs will appear in only 1 SOC.

The planned summaries for AEs are provided in Table 4.2**Error! Reference source not found.**.

Table 4.2. Tables and Listings Related to Adverse Events

Analysis	Details	Analyses
Overview of AEs	The number and percent of participants with: • At least 1 TEAE • SAE • death, and • permanent discontinuation from study intervention due to an AE.	Overall and Induction Analyses
TEAEs by PT within SOC	The number of participants, percent of participants, and IR of TEAEs using MedDRA PT nested within SOC. SOCs will be ordered by the difference in IRs between all LY and placebo.	Overall and Induction Analyses
Maximum Severity TEAEs by PT	The number and percent of participants with TEAEs by maximum severity using MedDRA PT. For each participant and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. The maximum severity will be determined based on the nonmissing severities. If all severities are missing for the defined postbaseline period of interest, it will show as missing in the table. Events will be ordered by risk difference (total LY versus placebo) within SOC. SOCs will be listed by risk difference.	Induction Analysis
TEAEs occurring at ≥5% by PT	The number of participants, percent of participants, and IR of TEAEs using MedDRA PT occurring in ≥5% before rounding. Events will be ordered by decreasing difference in IRs.	Induction Analysis
Listing of AEs leading to permanent discontinuation of study intervention	Primary AE listed on the disposition form will be used and planned treatment group will be listed.	--
Listing of AEs leading to permanent discontinuation from study	Primary AE listed on the disposition form will be used and planned treatment group will be listed.	--
Listing of SAEs	SAEs resulting in death will be identified through a flag in the listing and planned treatment group will be listed.	--

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Abbreviations: AE = adverse event; IR = incidence rate; LLT = Lowest Level Term; LY = Lilly product number; MedDRA = Medical Dictionary for Drug Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

4.6.3. Narratives

The following are "notable" events, from start of study intervention through end of study participation (or data cutoff for the submission if earlier):

- deaths
- serious AEs
- other AEs judged to be of clinical importance by Lilly, and
- permanent discontinuations of study intervention due to AEs.

Narratives (patient-level data and summary paragraph) will be provided for participants in the safety population with at least 1 notable event.

Safety topics of interest are not considered notable events, unless 1 of the above criteria is met. Displays with individual participant-level data will be created for safety topics of interest using various formats such as a customized listing and/or a customized graphical patient profile as specified in the section associated with the safety topic of interest. Medical case summaries or vignettes will be provided if deemed relevant for the discussion of the safety topic of interest.

4.6.4. Device Product Complaints (if applicable)

The ISA-SAP will identify whether a listing for device product complaints is necessary. The listing will include, as a minimum, the device product complaint that led to an AE or that could have led to a serious AE had intervention not been taken.

4.6.5. Additional Safety Assessments

Sections 4.6.5.1 through 4.6.5.5 specify additional safety analyses for all ISAs for clinical laboratory evaluations, vital signs, hepatic safety, infections, and malignancy. Section 4.6.5 of the ISA-SAP may clarify these analyses or specify additional analyses of interest.

4.6.5.1. Clinical Laboratory Evaluations

Summaries will be created for the laboratory analyte measurements as noted in Table 6.3. The planned summaries are provided in Table 4.3.

Baseline and postbaseline values are defined as follows:

- **last baseline:** the last nonmissing observation in the baseline period; unplanned measurements will be excluded
- **last postbaseline:** last nonmissing observation in the postbaseline period; unplanned measurements will be excluded
- **maximum baseline:** maximum nonmissing value during the baseline period; planned and unplanned measurements will be included

- **maximum postbaseline:** maximum nonmissing observation during the postbaseline period; planned and unplanned measurements will be included
- **minimum baseline:** minimum nonmissing value during the baseline period; planned and unplanned measurements will be included, and
- **minimum postbaseline:** minimum nonmissing observation during the postbaseline period; planned and unplanned measurements will be included.

Box plots evaluate trends over time and assess the potential impact of outliers on central tendency summaries. Summaries and analyses of minimum and maximum values are used to identify laboratory analytes that have an imbalance in the most extreme values and extreme changes, which would indicate further investigation is required.

Table 4.3. Tables and Figures for Clinical Laboratory Evaluations

Analysis Type	Analysis Details	Sample
Box plots and mean/SD plots for observed values by visit	Includes participants who have both a baseline and at least 1 postbaseline measurement from a planned visit. Unplanned measurements will be excluded. Last baseline will be used. Original-scale data will be used. Both SI and conventional units will be provided in the axis within a single plot. No inferential statistics.	Overall Analysis
Box plots and mean/SD plots for change from baseline values by visit	Includes participants who have both a baseline and at least 1 postbaseline measurement from a planned visit. Unplanned measurements will be excluded. Last baseline will be used. No inferential statistics.	Overall Analysis
Participants with elevated or low values meeting specified levels	Excludes analytes collected qualitatively. Definitions of low and high values in Tables 59 and 60 from FDA's Standard Safety Tables and Figures Integrated Guide will be used for the numerator[a]. Includes participants with at least 1 postbaseline measurement. Maximum baseline is used for elevated assessments and minimum baseline is used for low assessments. See Table 24 from FDA's Standard Safety Tables and Figures Integrated Guide[a].	Overall Analysis
Listing of abnormal laboratory findings	Includes laboratory analytes collected quantitatively (high or low during postbaseline using Level 2 definitions; see FDA's Standard Safety Tables and Figures Integrated Guide[a]) and qualitatively (abnormal during postbaseline). Includes participant identification, treatment group, laboratory analyte collection day (that is, days from start of study intervention), analyte name, and analyte finding.	Overall Analysis

Abbreviations: SD = standard deviation; SI = international system of units.

[a] CDER/BIRRS 2022.

Scatter plots to support clinical laboratory evaluations

Scatter plots of maximum-by-maximum measurements and minimum-by-minimum measurements will not be created a priori. They may be created if warranted after review of the planned tables and figures, using Figures 6.3 and 6.4 from the Analysis and Displays for Labs white paper (PHUSE 2022) as the model. Analysis Data Model datasets will include variables to enable the creation of scatter plots for use in either an interactive tool or for ad hoc figures.

4.6.5.2. Vital Signs, Physical Findings, and Other Observations Related to Safety

The definitions for last/maximum/minimum baseline/postbaseline provided in Section 4.6.5.1 also apply to this section.

The planned summaries are provided in Table 4.4. The measurements analyzed for vital signs and physical characteristics include systolic blood pressure, diastolic blood pressure, pulse, weight, and temperature.

Table 4.4. Tables and Figures for Vital Signs and Physical Characteristics

Analysis Type	Analysis Details	Sample
Box plots and Mean/SD plots for observed values by visit	Includes participants who have both a baseline and at least 1 postbaseline measurement from a planned visit. Unplanned measurements will be excluded. Last baseline will be used. No inferential statistics.	Overall Analysis
Box plots and Mean/SD plots for change from baseline values by visit	Includes participants who have both a baseline and at least 1 postbaseline planned measurement. Unplanned measurements will be excluded. Last baseline will be used. No inferential statistics.	Overall Analysis
Participants with elevated or low values meeting specified levels, vital signs	Definitions provided in Tables 31-33 from FDA's September 2022 Standard Safety Tables and Figures Integrated Guide will be used for the numerator[a]. Includes participants with at least 1 postbaseline measurement.	Overall Analysis

Abbreviations: SD = standard deviation.

[a] CDER/BIRRS 2022.

Scatter plots to support vital sign evaluations

Scatter plots of maximum-by-maximum measurements and minimum-by-minimum measurements will not be created a priori. They may be created if warranted after review of the planned tables and figures, using Figures 6.3 and 6.4 from the Analysis and Displays for Labs white paper (PHUSE 2022) as the model. Analysis Data Model datasets will include variables to enable the creation of scatter plots for use in either an interactive tool or for ad hoc figures.

4.6.5.3. Hepatic Safety

Hepatic labs include alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, serum alkaline phosphatase, international normalized ratio, and gamma-glutamyltransferase. When criteria are met for hepatic evaluations, investigators will conduct close monitoring of hepatic symptoms and liver tests, perform a comprehensive evaluation for alternative causes of abnormal liver tests, and complete follow-up hepatic safety eCRFs.

Table 4.5 describes the planned summary tables related to hepatic safety.

Table 4.5. Summary Tables and Figures Related to Hepatic Safety

Analysis	Sample
Abnormal Postbaseline Categories – Hepatic Safety Parameters • ALT: The number and percentage of participants with a measurement greater than or equal to 1 time (1X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) the performing lab ULN during the treatment period for all participants with a postbaseline value. • AST: The number and percentage of participants with a measurement greater than or equal to 1 time (1X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) the performing lab ULN during the treatment period for all participants with a postbaseline value. • ALP: The number and percentage of participants with a measurement greater than or equal to 2 times (2X), and 3 times (3X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline. • TBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2X), 5 times (5X), and 8 times (8X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value. • DBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2X) and 5 times (5X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value. • GGT: The number and percentage of participants with a measurement greater than or equal to 2 times (2X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.	Overall Analysis
Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs. ALT or AST)	Overall Analysis
Cholestatic Drug-Induced Liver Injury Screening Plot (TBL vs. ALP)	Overall Analysis

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; DBL = direct bilirubin; GGT = gamma-glutamyltransferase; TBL = total bilirubin; ULN = upper limit of normal.

4.6.5.4. Infections

For each reported AE of infection, investigators will complete a Follow-Up Form. The form solicits additional information about the reported infections, including details about the laboratory data and clinical specimens used in making the diagnosis; this additional information

facilitates a more thorough medical review and aids in understanding of individual cases, including the strength of the diagnosis. Prior to database lock, reported infection AEs will be coded to PTs, using all the PTs from the Infections and Infestations SOC as defined in MedDRA.

TE confirmed opportunistic infections (OIs) will be identified in a step-wise manner:

1. Identify potential TE OIs
    a. PTs corresponding to potential TE OIs are listed in a document separate from this SAP. The list is updated with each new version of MedDRA. When the PT list is updated based on new versions of MedDRA, this will not necessitate an update to this SAP. The PT lists are maintained through a separate process.
2. Prior to the database lock, GPS and medical will review the infection-specific CRF and determine whether a potential TE OI qualifies as a confirmed TE OI. TE infections meeting modified criteria for OIs from Winthrop et al. (2015) will qualify as a confirmed TE OI. The modified Winthrop criteria is:
    a. Candidiasis infections involving the oral cavity and pharynx are not considered OIs. For such an event to be classified as an OI, diagnostic evidence must confirm infection of either the esophagus or GI tract below the esophagus.
    b. Localized herpes zoster infections are not considered OI. Only multidermatomal infections, disseminated infections, or both are considered OI.
        i. Localized or nonmultidermatomal are defined as involvement of the primary and/or adjacent dermatomes only. These may be complicated or uncomplicated:
            1. Complicated: documented ocular (cornea or deeper structure; for example, iritis, keratitis, retinitis, and so on) or motor nerve involvement (for example, palsy). Postherpetic neuralgia does not meet criteria for motor nerve involvement.
            2. Uncomplicated: localized or nonmultidermatomal cases that are not complicated.
        ii. Multidermatomal is defined as involvement beyond primary and adjacent dermatomes (that is, 4 or more contiguous dermatomes) or involvement of 2 or more noncontiguous dermatomes. These may be complicated or uncomplicated.
            1. Complicated: documented ocular (cornea or deeper structure; for example, iritis, keratitis, retinitis, and so on) or motor nerve development.
            2. Uncomplicated: multidermatomal cases.
        iii. Disseminated: systemic infection, visceral, or widespread cutaneous (for example, 5 or more dermatomes or from 3 to 4 dermatomes including at least 1 noncontiguous [nonadjacent]).
    c. TE, active tuberculosis infection is an OI.

Table 4.6 describes the planned summary tables related to infection safety.

Table 4.6. Summary Tables, Figures, and Listings Related to Infection Safety

Analysis	Details	Sample
Summary of TE Infections	The number and percent of participants with ≥1 TE infection, serious infection (death or SAE), temporary or permanent discontinuation of study intervention due to infection, TE OI, and TE infections of interest.	Induction and Overall Analyses
TE Infections – Infections of Interest	The number of participants, percent of participants, and IRs for participants with ≥1 TE infection of interest, maximum severity, serious infection (death or SAE), temporary or permanent discontinuation of study intervention, and whether the event is ongoing or resolved. TE infections of interest: upper respiratory infection, herpes zoster, other herpes infections, conjunctivitis, and candida.	Induction Analysis
Listing of Serious Infections	Includes participant identification, treatment group, SOC/PT, event start date, severity, action taken, relationship to study treatment or non-study treatment, and whether the SAE caused discontinuation.	--
Listing of TE OIs	Includes participant identification, treatment group, SOC/PT, event start date, severity, action taken, relationship to study treatment or non-study treatment, and whether the SAE caused discontinuation.	--

Abbreviations: TE = treatment-emergent; OI = opportunistic infection; IR = incidence rate; SOC = System Organ Class; PT = Preferred Term; SAE = serious adverse event.

4.6.5.5 Malignancy

A listing of TE malignancies regardless of type (that is, including non-melanoma skin cancers) will be reported.

4.7. Other Analyses

Section 4.7.1 describes subgroup analyses, while Section 4.7 of the ISA-SAP will specify additional analyses of interest.

4.7.1. Subgroup Analyses

Subgroup analyses will be performed on the primary endpoint/estimand(s) and may be performed on key secondary endpoints and/or estimands. The variables for subgroup analyses are specified in Table 6.1.

4.8. Interim Analyses

Section 4.8 of the ISA-SAP will describe the interim analysis plan.

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4.9. Changes to Protocol-Planned Analyses

No changes to the analyses specified in Protocol IMMB.

5. Sample Size Determination

See the ISA or the ISA-SAP for information on the sample size determination.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized in the mITT population by treatment group. The summary will include descriptive statistics such as the number of participants, mean, standard deviation, median, minimum, maximum for continuous measures, and frequency counts and percentages for categorical measures. No formal statistical comparisons will be made among treatment groups.

Depending on the study design of the ISA, the ISA-SAP may specify additional analyses for characterizing the maintenance period.

The demographic and baseline characteristic variables outlined in Table 6.1 will be summarized across ISAs. Table 6.1 identifies variables with *a priori* interest for subgroup analyses although ISAs are not required to report subgroup analyses; see the ISA-SAP for more information.

Table 6.1. Demographic and Baseline Characteristic Variables

Variable	Quantitative	Categorical Summary	Subgroup Analysis
Age[a]	Yes	<35, 35-<50, 50-<65, ≥65	Yes
Height	Yes		
Weight	Yes		
BMI (kg/m^2)	Yes		
Sex	No	Female, Male	Yes
Race	No		
Country	No	[Depends on ISA. Puerto Rico is included in the United States]	Yes
Prior AD treatments	No	None, Topicals (TCS, TCI, JAK inhibitors, PDE4 inhibitors), Phototherapy or Photochemotherapy, Systemic Corticosteroids, Systemic Immunosuppressives, Advanced Biologics and/or Small Molecules for AD	
vIGA-AD	No	3, 4	Yes
EASI	Yes	<20, 20-<30, ≥30	Yes
BSA	Yes		
SCORAD	Yes		
Itch NRS	Yes	<4, ≥4	Yes

Abbreviations: AD = atopic dermatitis; BMI = body mass index; BSA = body surface area; EASI = eczema area and severity index; eCRF = electronic case report form; JAK = Janus kinase; NRS = numeric rating scale; PDE4 = phosphodiesterase-4; SCORAD = SCORing atopic dermatitis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.

[a] Age will be calculated using an imputed date of birth of July 1st in the year of birth collected in the eCRF. It will be calculated as: Age (in years) = (date of first dose – imputed date of birth) / 365.25.

6.2. Appendix 2: Definition of Efficacy Endpoints and Patient-Reported Health Outcomes

Table 6.2 provides the derivation of efficacy and patient-reported health outcomes common across the ISAs. The ISA-SAP will provide additional derivations for ISA-specific outcomes (for example, the asthma control questionnaire in Study J4E-MC-FR01).

Table 6.2. Derivation of Efficacy and Patient-Reported Health Outcomes

Measure	Variable	Derivation / Comment	Approach if Missing Components
vIGA-AD	vIGA-AD Score	Single item in integers from 0 to 4: • 0 represents 'clear' • 4 represents 'severe'	--
	vIGA-AD of 0 or 1	Observed score of 0 or 1.	--
EASI	EASI Score	Derive EASI region score for each of head and neck, trunk, upper limbs, and lower limbs as follows: $EASI_{region}$ = (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. Total EASI score is: $EASI = 0.1*EASI_{head\ and\ neck} + 0.3*EASI_{trunk} + 0.2*EASI_{upper\ limbs} + 0.4*EASI_{lower\ limbs}$	If value from percentage involvement is 0, then corresponding EASI region score is 0 even if erythema, edema/papulation, excoriation, and/or lichenification are missing. Otherwise, EASI score is missing if any component is missing.
	Change from baseline	Observed EASI score – baseline EASI score	Missing if baseline or observed is missing.
	Percent change from baseline	$100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed is missing.
	EASI-XX For XX = 50, 75, and 90	% change from baseline ≤-XX	Missing if baseline or observed is missing.
SCORAD	SCORAD score	SCORAD = A/5 + 7B/2 + C, where A is extent of disease, range 0-100 B is disease severity, range 0-18 C is subjective symptoms, range 0-20	Missing if component A, B, and/or C are missing.
	Change from baseline	Observed SCORAD score – baseline SCORAD score	Missing if baseline or observed is missing.
	Percent change from baseline	$100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed is missing.
	SCORAD-XX For XX = 50, 75, and 90	% change from baseline ≤-XX	Missing if baseline or observed value is missing.

Approved on 15 Aug 2023 GMT

Measure	Variable	Derivation / Comment	Approach if Missing Components
Itch NRS	Itch NRS Score	The (prorated) mean based on the prior 7 days. For example, if a participant only had 3 days, then the itch NRS score is the mean of the 3 non-missing days, range 0-10. The ISA-SAP maps the daily dairy entries to study visits.	Baseline: Missing if more than 3 days from prior week are missing. Post-Baseline: Missing if all days from prior week are missing.
	Change from baseline	Observed itch NRS score – baseline itch NRS score	Missing if baseline or observed value is missing.
	4-point improvement	Change from baseline ≤-4	Missing if baseline or observed value is missing
Skin Pain NRS	Skin Pain NRS Score	The (prorated) mean based on the prior 7 days. For example, if a participant only had 3 days, then the skin pain NRS score is the mean of the 3 non-missing days, range 0-10. The ISA-SAP maps the daily dairy entries to study visits.	Baseline: Missing if more than 3 days from prior week are missing. Post-Baseline: Missing if all days from prior week are missing.
	Change from baseline	Observed skin pain NRS score – baseline skin pain NRS score	Missing if baseline or observed value is missing.
	4-point improvement	Change from baseline ≤-4	Missing if baseline or observed value is missing.
POEM	POEM score	Sum of questions 1 to 7, range 0-28.	Missing if all questions are left unanswered. Otherwise, a prorated mean is used: mean score of answered questions times 7. If more than one response is selected, the response with the highest score is used.
	Change from baseline	Observed POEM score – baseline POEM score	Missing if baseline or observed value is missing.

Measure	Variable	Derivation / Comment	Approach if Missing Components
	4-point improvement	Change from baseline ≤-4	Missing if baseline or observed value is missing
DLQI	DLQI total score	A DLQI total score is calculated by summing all 10 question responses, range 0-30.	Missing if any question is unanswered. Note: For questions 3-10, 'Not relevant' is scored as a 0.
	Change from baseline	Observed DLQI total score – baseline DLQI total score	Missing if baseline or observed is missing.
	4-point improvement	Change from baseline ≤-4	Missing if baseline or observed value is missing.
ADCT	ADCT score	Sum of questions 1 to 6, range 0-24.	Missing if any question is left unanswered.
	ADCT ≥7 (Not in control)	Observed ADCT score ≥7	--
	Change from baseline	Observed ADCT score – baseline ADCT score	Missing if baseline or observed value is missing.
	5-point improvement	Change from baseline ≤-5	Missing if baseline or observed value is missing.

Abbreviations: ADCT = Atopic Dermatitis Control Tool; DLQI = Dermatology life quality index; EASI = eczema area and severity index; ISA-SAP = intervention specific appendix-statistical analysis plan; NRS = numeric rating scale; POEM = Patient-Oriented eczema measure; SCORAD = SCORing atopic dermatitis; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.

6.3. Appendix 3: Laboratory Analytes for Safety Analyses

Table 6.3 lists the laboratory analytes of interest across each ISA. ISA-SAPs may specify additional laboratory analytes of interest.

Table 6.3. Laboratory Analytes

Laboratory Group	Parameter
General Chemistry	Sodium
	Potassium
	Chloride
	Bicarbonate
	Blood urea nitrogen
	Glucose
	Calcium
	Protein
	Albumin
Kidney Function	Creatinine
	eGFR
Liver Biochemistry	Alkaline phosphatase
	Alanine aminotransferase
	Aspartate aminotransferase
	Bilirubin
Complete Blood Count	WBC
	Hemoglobin
	Platelets
WBC Differential	Lymphocytes
	Neutrophils
	Eosinophils
Coagulation Studies	PT
	PTT

Abbreviations: eGFR = estimated glomerular filtration rate; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell.

7. References

[CDER/BIRRS] Center for Drug Evaluation and Research, Biomedical Informatics and Regulatory Review Science Team. FDA Standard Safety Tables and Figures: Integrated Guide. August 2022. Accessed July 26, 2023.

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