Statistical Analysis Plan J4E-MC-FR01 (Version 3)

A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

NCT05911841

Approval Date: 07-May-2025

Title Page

Master 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

Master Protocol Number: J4E-MC-IMMB

ISA Title: A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

ISA Number: J4E-MC-FR01

Compound Number: Ucenprubart (LY3454738)

ISA Short Title: A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

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Version history

This is the intervention-specific appendix statistical analysis plan (ISA-SAP) for Study J4E-MC-FR01 (FR01) and supplements the master protocol SAP (MP-SAP) for Study J4E-MC-IMMB (IMMB) and is based on the protocol dated 06MAY2024. This SAP was finalized before first unblinding to study team, or efficacy or safety unblinding.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	04 Nov 2024	Not Applicable	Original version
2	See Date on Page 1	Added adjustment for baseline value in the ANCOVA	Version 2.0 updated prior to the DBL date on Nov 07 2024.
3	See Date on Page 1	Added adjustment for individuals randomized prior to protocol amendment c vs after protocol amendment c.	Randomization ratio in biologic-and-small-molecule experienced population has been changed.

1. Introduction

This is an ISA-SAP for Study FR01 that supplements the SAP for the atopic dermatitis master protocol (Study IMMB).

There are no changes to the analyses described in the protocol.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To compare the efficacy of LY3454738 versus placebo as measured by EASI-75 in the treatment of CCI [redacted] with moderate-to-severe AD	Proportion of participants achieving EASI-75 at Week 16
Secondary	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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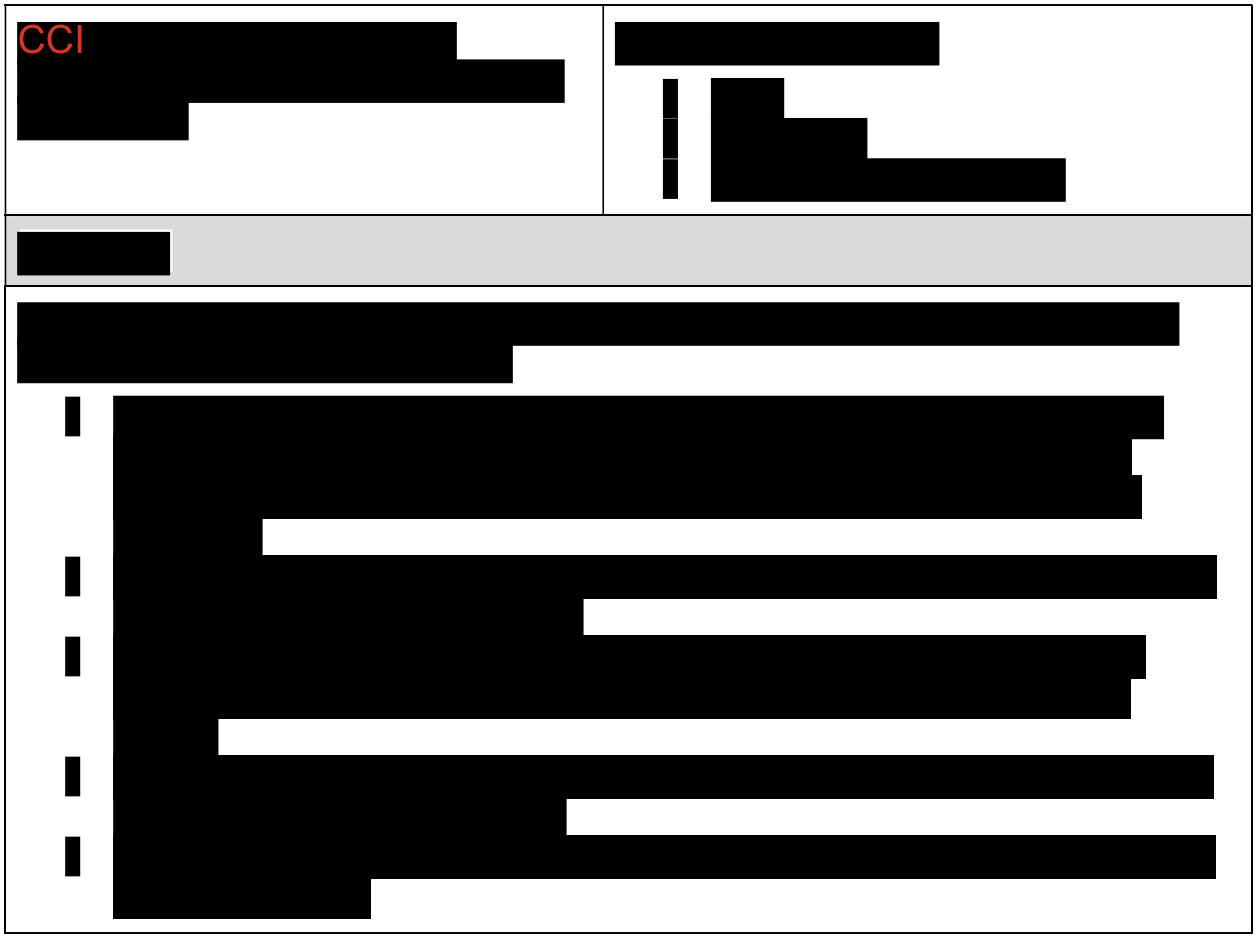

Abbreviations: CCI AD = atopic dermatitis; ADA = antidrug antibodies; CCI vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis.

Most primary, secondary, and exploratory estimands are stated for efficacy assessments in the biologic-and-small-molecule-naïve participant population, and safety assessments during the maintenance period. The estimands for the overall population and the biologic-and/or-small-molecule-experienced population will use similar estimands with the relevant change to the population (see Section 6.2, Appendix B for additional information).

The MP-SAP specifies the estimands for overall and induction-specific safety assessments.

Primary estimand: composite

The primary clinical question of interest is: in the target patient population, what is the difference between each dosing regimen of LY3454738 and placebo in achieving a successful response at Week 16 without use of any prohibited or rescue medication for atopic dermatitis (AD), or early permanent discontinuation of study intervention?

The estimand is described by these attributes:

- Populations: CCI [redacted] with moderate-to-severe AD
- Endpoint: the primary endpoint and all secondary efficacy endpoints, that is, Eczema Area and Severity Index (EASI)-75, CCI [redacted]
- How to account for intercurrent events (ICEs):
  - A composite strategy will be used for all types of ICEs CCI [redacted]
- Population-level summary:
  - For binary endpoints CCI [redacted] the population-level summary will be the difference in response rate at CCI between each dosing regimen of LY3454738 and placebo.
  - For continuous endpoints (percent change from baseline in EASI CCI [redacted], mean difference at Week 16 between each dosing regimen of LY3454738 and placebo.
- Rationale for estimand: the composite estimand is the standard for prior AD studies CCI [redacted] From the perspective of ICEs:
  - If a participant used any prohibited or rescue medication for AD, the participant was not receiving sufficient benefits from study intervention.
  - If a participant early discontinued study intervention, the participant experienced a burden of study intervention that outweighed its benefits.

Secondary estimand for safety during the maintenance period

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 during the maintenance treatment period?

The estimand is described by these attributes:

- Population: participants with moderate-to-severe AD.
- Endpoint: number, percent, and/or IRs for the first TEAE of interest.
- How to account for ICEs:
  - Early permanent discontinuation of study intervention: TEAEs during the post-treatment 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, regardless of relation to AD, will be considered attributable to the study intervention.
    - Assignment to escape arm: if a participant escapes from placebo to LY3454738, subsequent TEAEs will be considered attributable to LY3454738.
    - Assignment to placebo withdrawal arm: if a participant is re-randomized from LY3454738 to placebo, TEAEs will be considered attributable to LY3454738.
- Population-level summary: the difference in IRs for TEAEs of interest between participants receiving (rather than assigned to) LY3454738 versus placebo.
- Rationale for estimand: TEAEs during the maintenance and posttreatment follow-up periods will help inform the safety profile of maintenance dosing in the context of the overall safety profile.

Exploratory efficacy estimand for effect of rescue medication (rescue medication effect estimand)

An exploratory clinical question of interest is: what is the difference between each dosing regimen of LY3454738 and placebo in the target patient population in achieving a successful response at Week 16 without use of prohibited medication for AD, or early discontinuation of study intervention?

The estimand is described by these attributes:

- Population: CCI [redacted] with moderate-to-severe AD.
- Endpoint: the primary endpoint and select secondary efficacy endpoints, that is, CCI [redacted].
- How to account for ICEs:
    - A hybrid strategy will be used for ICEs:
        - Early discontinuation of study intervention: a composite strategy will be used. That is, participants with early treatment discontinuation will be considered as a treatment failure.
        - Use of prohibited medication for AD: a composite strategy will be used. That is, participants will be considered a treatment failure after using prohibited medication for AD.
        - Use of rescue medication for AD: a treatment policy strategy will be used. That is, observed data will be used.
- Population-level summary: the difference in response rate at Week 16 between each dosing regimen of LY3454738 and placebo.
- Rationale for estimand:
    - If a participant discontinued from treatment early, the participant did not experience a sufficient risk-benefit of study intervention.
    - If a participant started prohibited medication other than topical corticosteroid (TCS) for AD, the participant experienced a burden of study intervention that

outweighed its benefits. Additionally, the study intervention is unlikely to be combined in practice with other AD medications besides TCS.

- If a participant started rescue medication (TCS), the participant may not have experienced sufficient benefit from the study intervention alone, started the standard-of-care add-on treatment for AD, and LY3454738 may have provided more of a benefit in combination with rescue medication than rescue medication alone. This approach is particularly relevant because LY3454738 may be combined in practice with TCS.

1.2. Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient dose-ranging study to evaluate the efficacy and describe the safety of multiple LY3454738 induction and maintenance dosing regimens in adult participants with moderate-to-severe AD.

- Study population
  - Adults with moderate-to-severe AD: EASI ≥16, vIGA-AD score ≥3, and ≥10% body surface area (BSA) involvement at randomization.
  - Includes CCI participants.

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- Concomitant therapy
  - TCS use: prohibited unless participant does not respond to the assigned study intervention in specific circumstances.
  - Rescue medication: participants without an CCI response at Week 16, or an CCI response at CCI, are assigned to LY3454738 CCI mg CCI.
  - Other concomitant therapy for the purpose of AD is prohibited.

2. Statistical Hypotheses

The primary objective is to demonstrate that at least one LY3454738 dose is superior to placebo in achieving EASI-75 [*outcome*] at Week 16 [*timepoint*] without using any prohibited or rescue medication for AD or early discontinuation of study intervention [*estimand*] in CCI [redacted] participants [*population*]. Thus, the null hypothesis to be tested in relation to the *primary composite* estimand is:

- Null hypothesis: No LY3454738 dose is different from placebo with respect to the achievement of EASI-75 [*outcome*] at Week 16 [*timepoint*].

The statistical test will be 2-sided and will be performed at a significance level of 0.05. No adjustments for multiplicity will be performed.

The statistical hypotheses for the secondary and exploratory endpoints and estimands are similar to the primary hypothesis with the *outcome*, *timepoint*, *estimand*, or *population* appropriately modified; see Section 6.2, Appendix B for more information.

2.1. Multiplicity Adjustment

No adjustment for multiplicity will be performed.

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3. Analysis Sets

Table FR01.3.1 describes the population and determination of treatment assignment for efficacy and safety analyses. Table FR01.3.2 describes the sets of data points for each estimand. Section 6.2, Appendix B provides more information on the analysis sets and data points sets used in efficacy analyses, including the relevant population, endpoint, and estimand information.

For interim analyses, the induction analysis set will include participants who could have completed the Week 16 visit. This is specifically defined as those with an analysis data cut date – randomization date +1 ≥ 116 days. The maintenance analysis set will include participants who enter the maintenance period without being assigned to the escape arm at Week 16 and could have completed Week 44.

Table FR01.3.1. Analysis Sets for Evaluation of Induction and Maintenance Efficacy

Analysis Set	Description	Populations	Analyses Conducted on This Analysis Set
Induction Analysis Set	All randomized participants who receive at least 1 dose of study intervention. Participants will be included in the analysis set according to their randomly assigned intervention.	• Overall CCI	• vIGA-AD • EASI • SCORAD CCI • PROs
Maintenance Analysis Set	All randomized participants who enter the maintenance period without being assigned to the escape arm at Week 16. Participants will be included in the analysis set according to their randomly assigned intervention.	• Overall CCI	• vIGA-AD • EASI • SCORAD CCI • PROs
Maintenance Escape Analysis Set	All randomized participants who enter the maintenance period and are assigned to the escape arm at Week 16. Participants will be included in the analysis set according to their randomly assigned intervention.	• Overall	• vIGA-AD • EASI • SCORAD • Itch NRS • PROs
Safety	All randomized participants receiving at least 1 dose of study intervention. Participants will be included in the analysis according to the intervention they actually received.	• Overall CCI	Safety data analyses for induction or maintenance period

Pharmacokinetics (PK)	All randomized participants receiving at least 1 dose of study intervention and have PK data available.	• Overall	PK data analyses for induction and/or maintenance period

Abbreviations: EASI = Eczema Area and Severity Index; Itch NRS = Itch Numeric Rating Scale; PK = pharmacokinetics; PROs = patient-reported outcomes; SCORAD = Scoring Atopic Dermatitis; vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis.

Table FR01.3.2. Data Points Sets for Efficacy Analyses

Only data from planned visits or within the tolerance window of a visit will be included.

Data Points Sets	Description
Composite Induction DPS	• Prior to use of prohibited or rescue medication for AD and early permanent discontinuation of study intervention, observed data up to and including Week 16 will be included. • Upon use of prohibited or rescue medication for AD, and/or early permanent discontinuation of study intervention, participant visits up to and including Week 16 will be imputed as a nonresponder for binary endpoints and having no change from baseline for continuous endpoints. • Missed visits or visits with missing data after imputation for other ICEs of interest, participant visits up and including Week 16 will be imputed as a nonresponder for binary endpoints and having no change from baseline for continuous endpoints.
CCI [redacted]	[redacted]
Composite Maintenance DPS	• Prior to use of prohibited or rescue medication for AD, early permanent discontinuation of study intervention, and assignment to escape arm, observed data up to and including Week 44 will be included. • Upon use of prohibited or rescue medication for AD, early permanent discontinuation of study intervention, and/or assignment to escape arm if relevant to analysis, participant visits will, up to and including Week 44, be imputed as a nonresponder for binary endpoints and having no change from baseline for continuous endpoints. • Missed visits or visits with missing data after imputation for other ICEs of interest, participant visits up to and including Week 44 will be imputed as a nonresponder for binary endpoints and having no change from baseline for continuous endpoints.

Abbreviations: AD = atopic dermatitis; DPS = data points sets; ICEs = intercurrent events.

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4. Statistical Analyses

4.1. General Considerations

See Section 4.1 of the MP-SAP for general considerations applicable across all ISAs. Study-specific considerations for Study FR01 are:

- Efficacy and patient-reported outcome analyses will adjust for CCI [redacted]. Efficacy and patient-reported outcome analyses for the overall population will also adjust for participant population (that is, CCI [redacted] participants). CCI [redacted]

For efficacy and patient-reported outcome analyses, CCI [redacted]

For binary endpoints, CCI [redacted] sex, for analyses with the overall population, CCI [redacted] and for analyses with CCI [redacted] (Ye et al. 2023). If the working model does not converge, the difference in the simple average will be used to estimate the unconditional difference between different doses of LY3454738 and placebo, and Wald test will be used to calculate the p-value. The treatment response rates, treatment differences versus placebo, and their corresponding 95% confidence intervals (CIs) will be provided.

For continuous endpoints, CCI [redacted] The treatment response, treatment difference versus placebo, and their corresponding 95% CIs will be provided.

For efficacy and patient-reported outcomes, baseline is defined as the last entry prior to the first dose. For post baseline values if there are multiple entries on the same day then the entry at the earlier time point will be used for that day. Table FR01.4.1. Description of Efficacy Estimands

Estimand	Analysis Strategy for Intercurrent Events	

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	Treatment Discontinuation	Rescue Medication	Prohibited Medication for AD	Assignment to Escape Arm[a]	Handling of Missing Data[b]
Composite (Primary)	Set to baseline	Set to baseline (BOCF)	Set to baseline (BOCF)	Set to baseline (BOCF)	NRI (binary) BOCF (continuous)
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD = atopic dermatitis; NRI = nonresponder imputation; BOCF = baseline observation carried forward.

a Assignment to escape arm is only relevant for analyses of maintenance efficacy.

b Handling of missing data is the missing data strategy after accounting for intercurrent events.

4.2. Participant Dispositions

In addition to the information outlined in Section 4.2 of the MP-SAP, participants entering the maintenance treatment period will be described. Specifically, the number of participants achieving EASI-50 at Week 16, the number of participants randomly assigned to or entering the maintenance treatment arms or the escape arm at Week 16, the number of participants assigned to the escape arm during the maintenance phase, and the number of participants who discontinued during the maintenance phase.

4.3. Primary (Composite) Estimand Analyses

The composite estimand will be used for the primary, secondary, and exploratory efficacy endpoints and analyses. This estimand uses the induction analysis set and composite induction data points sets (DPS) defined in Table FR01.3.1 and Table FR01.3.2, respectively. Section 1.1 provides additional details and the rationale for the primary estimand, and Section 6.2, Appendix B describes the analyses across the different endpoints.

4.3.1. Missing Data

For composite estimand analyses, participants with missing data after accounting for ICEs of interest will be imputed as nonresponders (NRI) for binary outcomes and considered as having no change from baseline or baseline observation carried forward (BOCF) for continuous outcomes.

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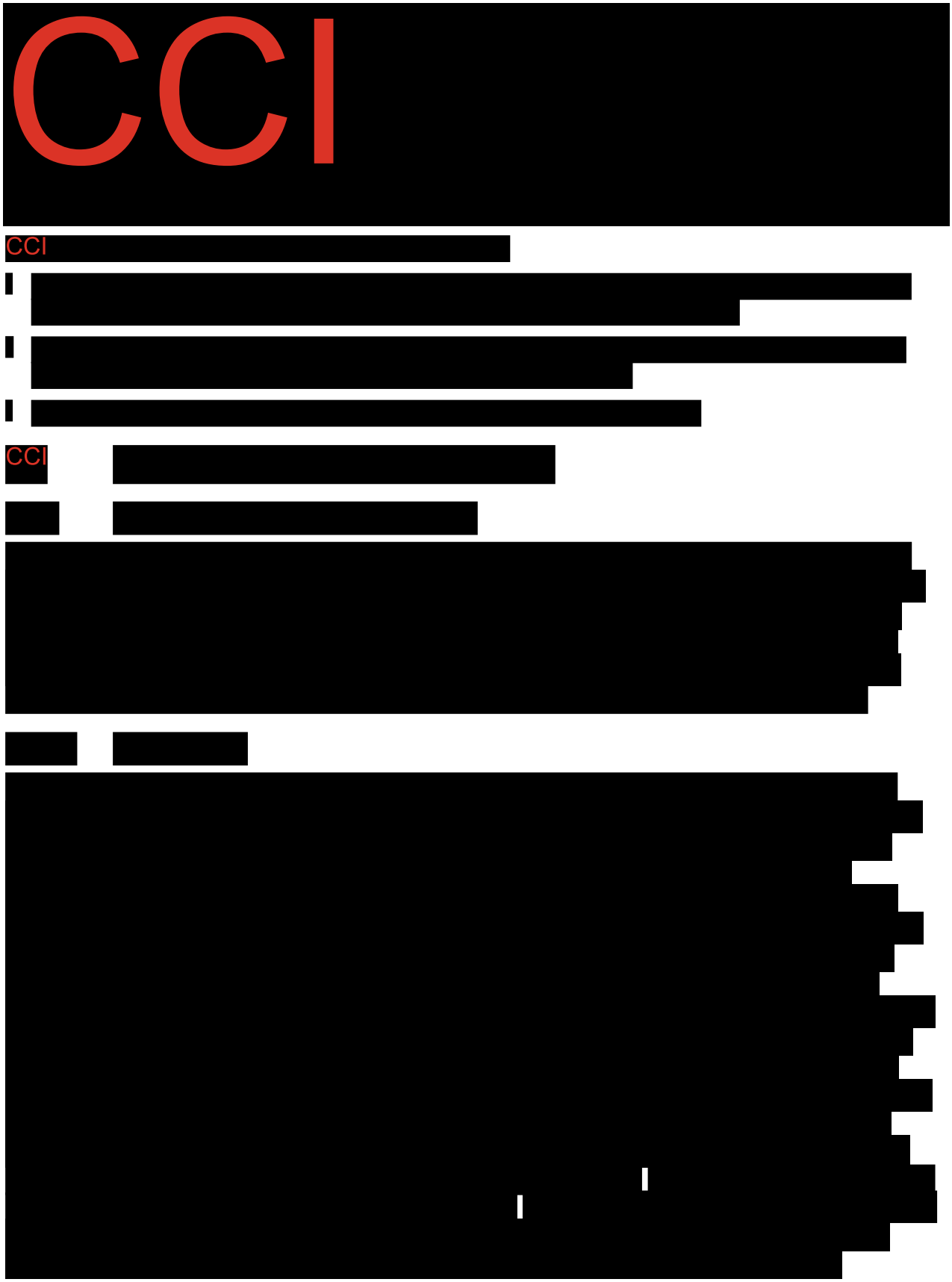
CCI
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CCI [redacted]

4.6. Safety Analyses

Section 4.6 of the MP-SAP details the baseline and postbaseline period definitions for the overall and induction safety analyses. Table FR01.4.3 provides the baseline and postbaseline period definitions for the maintenance safety analyses.

Table FR01.4.3. Baseline and Postbaseline Period Definitions for Safety Groups for the Maintenance Safety Analyses

Analysis Type	Baseline Period	Postbaseline Period
TEAEs (maintenance safety analyses)	*Randomized at Week 0:* Starts from the informed consent date for Study IMMB to just prior to the time of first dose in the maintenance treatment period. *Assigned to Escape Arm from Placebo (if applicable):* From the informed consent date for Study IMMB to just prior to the time of first dose of LY3454738 on the escape arm.	*Start Time* For participants randomized in the initial period: Starts at the time of first dose in the maintenance treatment period; that is, Week 16 (V16) or later. For participants assigned to the escape arm from placebo: Starts at the time of first dose of LY3454738 on the escape arm. *Stop Time* For participants randomized in the initial period to LY3454738 or assigned to the escape arm: Ends at the earliest of: • time of discontinuation from ISA • time of study completion, or • database cut-off date for ongoing studies. For participants initially randomized to placebo: Ends at the earliest of: • time of discontinuation from ISA • time of study completion • time of first dose on the escape arm, or • database cut-off date for ongoing studies.

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

4.6.1. Extent of Exposure

Extent of exposure to study drug will be summarized in the safety population by treatment group and treatment period (that is, extent of exposure will be summarized separately for the induction and maintenance periods). In the maintenance treatment period, the LY3454738 800 mg Q4W

and the escape arm will be considered the same treatment group. Days of exposure will be the date of last dose of study drug in either the induction or maintenance treatment period plus the dosing frequency (that is, 2 and 4 weeks for induction and maintenance treatment periods, respectively) minus the date of the first dose of study drug in the treatment period plus 1 day. The frequency and percentage of participants falling into different exposure ranges will be summarized. Exposure ranges for each treatment period are:

- Overall exposure: 0 to less than 4 weeks, 4 to less than 8 weeks, 8 to less than 12 weeks, 12 to less than 16 weeks, 16 to less than 24 weeks, 24 to less than 32 weeks, and at least 32 weeks,
- Induction treatment period: 0 to less than 4 weeks, 4 to less than 8 weeks, 8 to less than 12 weeks, and at least 12 weeks, and,
- Maintenance treatment period: 0 to less than 8 weeks, 8 to less than 16 weeks, and at least 16 weeks.

No p-values will be reported in these tables as they are intended to describe the exposure experience.

4.6.2. Adverse Events

Section 4.6.2 of the MP-SAP has the definition of TEAEs, and planned analyses for the overall and induction safety analyses. The planned summaries for the maintenance safety analyses are the same as the induction analyses specified in Section 4.6.2 of the MP-SAP.

4.6.3. Narratives

Section 4.6.3 of the MP-SAP describes the analysis plan for the narratives.

4.6.4. Device Product Complaints

A listing of all device product complaints, inclusive of device product complaints that led to an AE or that could have led to a serious adverse event (SAE) had intervention not been taken, will be included.

CCI [redacted]

[redacted]

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[redacted]

CCI

[redacted]

4.6.6. Additional Safety Assessments

Sections 4.6.5.1 through 4.6.5.5 of the MP-SAP specify additional safety analyses for clinical laboratory evaluations, vital signs, hepatic safety, infections, and malignancy.

4.6.6.1. Clinical Laboratory Evaluations

Section 4.6.5.1 of the MP-SAP describes the analysis plan for clinical laboratory evaluations. Appendix 3 of the MP-SAP provides a detailed list on the clinical laboratory evaluations of interest for Study FR01.

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

Section 4.6.5.2 of the MP-SAP describes the analysis plan for vital signs and physical findings.

4.6.6.3. Hepatic Safety

Section 4.6.5.3 of the MP-SAP describes the analysis plan for hepatic safety.

4.6.6.4. Infections

Section 4.6.5.4 of the MP-SAP describes the analysis plan for infections.

4.6.6.5. Malignancy

Section 4.6.5.5 of the MP-SAP describes the analysis plan for malignancies.

4.6.6.6. Systemic Hypersensitivity Reactions

A listing of all systemic hypersensitivity reactions will be provided.

4.6.6.7. Injection Site Reactions

Among reported injection site reactions (ISRs), the frequency and prevalence of the ISR dimension (for example, erythema, pain, and so on) and corresponding severity will be summarized by treatment group.

4.6.6.8. Conjunctivitis

Among reported conjunctivitis events, the frequency and prevalence of affected eye (that is, left, right, or both eyes), involvement of eye part (for example, eyelid), symptoms (for example, burning sensation), and severity will be summarized by treatment group.

4.6.6.9. Comorbid Allergic Diseases

The IRs of TEAE for specific comorbid allergic diseases of interest will be summarized in the overall safety analysis population: asthma (including allergic asthma), allergic conjunctivitis, food allergy, seasonal allergic rhinitis, perennial allergic rhinitis, chronic allergic rhinosinusitis, vitiligo, and celiac.

4.7. Other Analyses

4.7.1. Treatment Compliance

Treatment compliance with study intervention will be summarized by treatment arm and by treatment period. Overall compliance with therapy is defined to be missing no more than 20% of the expected doses and not missing 2 consecutive doses.

4.7.2. Subgroup Analyses

Subgroup analyses will be performed for EASI-75, vIGA-AD, and Itch NRS for the primary composite estimand at Week 16. The variables for the subgroup analyses are specified in Table 6.1 of the MP-SAP.

4.7.3. Analysis for Japan Submission

A subset of the planned efficacy, health outcomes, and safety analyses will be reproduced based on patients from Japan sites (Japanese population), in support of the regulatory submission in Japan. The list of tables, figures, and listings for the Japanese population will be provided in a separate document.

4.7.4. Actigraphy Analyses

The objective of this analysis is to assess treatment efficacy using digital measures with a focus on the nocturnal scratching and sleep disturbance. The actigraphy device, AX6, is being worn by study participants on both wrists during the nighttime. The raw device data will be processed and fed into an analytically validated algorithm to detect nocturnal scratch. Finally, digital endpoints will be extracted and can be used to quantify nocturnal scratching and sleep disturbance. Statistical analysis will be performed based on these digital endpoints to evaluate the effectiveness of the treated and placebo groups.

4.7.4.1. Actigraphy Data Description

Actigraphy data have been collected during four periods throughout Study FR01: Visit 0 (Week -2 to Week 0), Visit 6 to Visit 8 (Week 6 to Week 8), Visit 14 to Visit 16 (Week 14 to Week 16), Visit 40 to Visit 44 (Week 40 to Week 44). Only nighttime actigraphy data are being used for the purpose of analysis on nocturnal scratching and sleep disturbance.

4.7.4.1.1. Missing and Nonwear Device Data

All missing and nonwear period data are deleted without imputation. Nonwear (device is not on wrist) period is identified based on both temperature and non-movement detected by algorithm. For each participant at each study night, the digital endpoints are derived only from the hand which is wearing the device. If both hands are nonwear or missing, the participant-night is treated as missing.

4.7.4.1.2. Definition of Baseline and Postbaseline Measures

The actigraphy data collected from Visit 0 (Week -2 to 0) is used as the baseline value. The definition of baseline and postbaseline study visit mapping for actigraphy data is shown in Table FR01.6.3.

The baseline value for actigraphy endpoints is determined by the following algorithm:

1. Average the data within 7 days from both hands if at least 4 such days exist.
2. If not possible, average the data within 14 days from both hands if at least 4 such days exist.
3. If not possible, average the data within 14 days from either one or both hands if at least 4 such days exist.
4. If not possible, the baseline value is missing.

For treatment effect analysis that requires change from baseline, only participants with baseline device data available are included.

Postbaseline weekly actigraphy measures use a prorated weekly mean score, similar to the daily diary used for Itch NRS. If the participants have at least one day of digital endpoint measure, the weekly mean is the average of the available daily measures within the given week.

4.7.4.1.3. Digital Data Processing and Endpoints Calculation

Given the objective of actigraphy is assessing nocturnal scratch and sleep during the nighttime, the first step is to identify the total sleep opportunity (TSO) window. TSO window is defined as the period that subjects are trying to sleep and can be derived based on external open-source packages (van Hees et al. 2018, Mahadevan et al. 2021). Nonwear periods are removed prior to deriving TSO.

Nocturnal Scratch Digital Endpoints

The signal data are processed with steps including calibration, resampling, segmentation, and gravity removal. The signal timeseries data are segmented as a 3-second window and physics-based features are extracted from the signal data as input into the LightGBM model for binary scratch classification (Ji et al. 2023); CCI [redacted]

CCI [redacted]	[redacted]

CCI	

CCI

CCI	

Abbreviation: CCI

4.7.4.2. Statistical Analysis of Digital Endpoints

Analysis for each of the digital endpoints will be conducted in Sections 4.7.4.2.1 and 4.7.4.2.2.

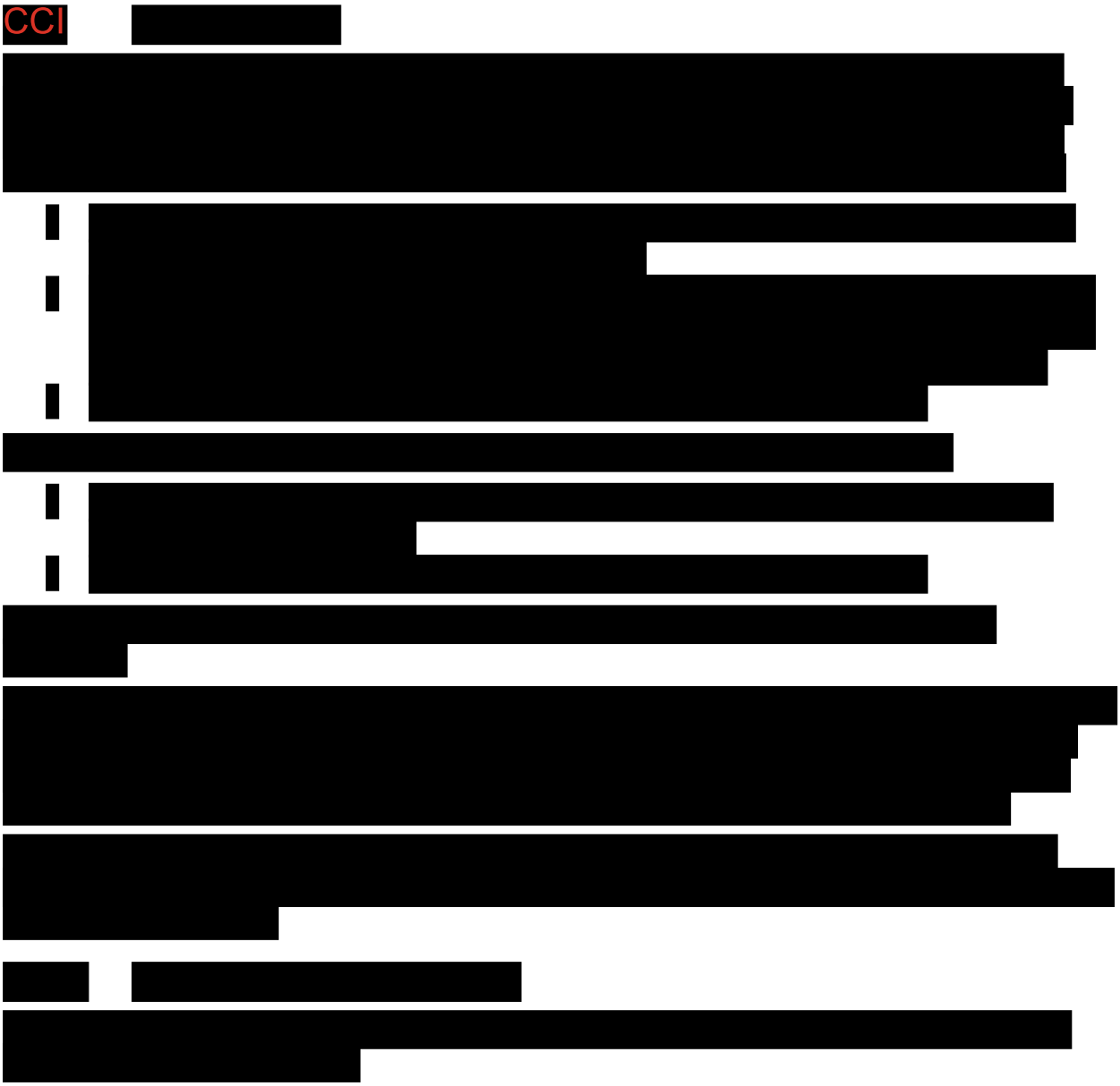
4.7.4.2.1. Correlation with Clinical Endpoints

CCI

4.7.4.2.2. Treatment Efficacy

The digital endpoints will be analyzed with the exploratory hypothetical estimand (see Table FR01.4.1) with the methodology specified in Section 4.1.

CCI [redacted]



4.7.6. Changes to Protocol-Planned Analyses

There are no changes to the protocol-planned analyses.

5. Sample Size Determination

Approximately 260 participants will be randomly assigned to the study intervention.

Of those, approximately 46% will be CCI individuals (n = 120). The remaining approximately 54% will be CCI individuals (n = 140). All randomized participants will be considered evaluable for the primary and secondary objectives.

The planned sample size for CCI participants are shown in this table by each induction dosing regimen.

Induction regimen	Approximate number of CCI participants planned	Approximate number of CCI participants planned	Approximate number of all participants planned
LY3454738 CCI mg CCI	56	40	96
LY3454738 CCI mg CCI	28	40	68
LY3454738 CCI mg CCI	28	0	28
Placebo	28	40	68

Abbreviation: CCI

With this planned sample size, an EASI-75 response at Week 16 of 52% and 12% for LY3454738 and placebo, respectively, in CCI participants achieves at least 91% power for pairwise comparisons with placebo using a 2-sided chi-square test at the 0.05 significance level, with no adjustment for multiple comparisons.

6. Supporting Documentation

6.1. Appendix A: Definition of Efficacy Endpoints and Patient-Reported Health Outcomes

Section 6.2 of the MP-SAP specifies the definition of the efficacy endpoints and patient-reported health outcomes common across the ISAs. Table FR01.6.1 specifies the endpoint definitions specific to Study FR01.

Table FR01.6.1. Derivation of FR01-Specific Efficacy and Patient-Reported Health Outcomes

Measure	Variable	Derivation / Comment	Approach if Missing Components
ACQ-5	ACQ-5 Total Score	Mean score of individual questions	Missing if more than 1 question is missing.
	Change from baseline	Observed ACQ-5 total score – baseline ACQ-5 total score	Missing if baseline or observed value is missing.
	MCID of 0.5	Change from baseline ≤ -0.5	Missing if baseline or observed value is missing.

Abbreviations: ACQ-5 = Asthma Control Questionnaire; MCID = minimal clinically important difference.

6.2. Appendix B: Description of Efficacy Analyses

Table FR01.6.2 presents the planned efficacy and patient-reported outcome analyses for the primary, secondary, and exploratory endpoints (excluding actigraphy and PK/PD analyses).

Table FR01.6.2. Planned Efficacy and Patient-Reported Outcome Analyses

Endpoint	Variable	Estimand	Analysis Set	DPS Set	CCI	Time (Weeks) [a]	Analysis Type
EASI	EASI-75	Composite	Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, **16**	Primary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
		Rescue Medication Effect	Induction Analysis Set	Rescue Medication Effect DPS		1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
		Composite	Induction Analysis Set	Composite Maintenance DPS		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
		Composite	Maintenance Analysis Set	Composite Maintenance DPS: Participants with EASI-50 Response at Week 16		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
				Composite Maintenance DPS: Participants with EASI-75 Response at Week 16		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
	CCI	Composite				1, 2, 4, 8, 12, CCI	Secondary

Endpoint	Variable	Estimand	Analysis Set	DPS Set	CCI	Time (Weeks) [a]	Analysis Type
			Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
	CCI	Composite	Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, CCI	Secondary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
		Composite	Maintenance Analysis Set	Composite Maintenance DPS: Participants with EASI-50 Response at Week 16		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
				Composite Maintenance DPS: Participants with EASI-75 Response at Week 16		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
	CCI	Composite	Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, CCI	Secondary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
Itch NRS	CCI	Composite	Induction Analysis Set	Composite Induction DPS: Participants with ≥4 itch NRS at baseline		1, 2, 4, 8, 12, CCI	Secondary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
		Rescue Medication Effect	Induction Analysis Set			1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory

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Endpoint	Variable	Estimand	Analysis Set	DPS Set	CCI	Time (Weeks) [a]	Analysis Type
				Rescue Medication Effect DPS: Participants with ≥4 itch NRS at baseline		1, 2, 4, 8, 12, 16	Exploratory
		Composite	Induction Analysis Set	Composite Maintenance DPS: Participants with ≥4 itch NRS at baseline		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
SCORAD	CCI	Composite	Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, CCI	Secondary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
		Composite	Induction Analysis Set	Composite Maintenance DPS		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
	CCI	Composite	Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, CCI	Secondary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
	CCI	Composite	Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, CCI	Secondary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
vIGA-AD	CCI	Composite	Induction Analysis Set	Composite Induction DPS		1, 2, 4, 8, 12, CCI	Secondary
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory

Endpoint	Variable	Estimand	Analysis Set	DPS Set	CCI	Time (Weeks) [a]	Analysis Type
		Rescue Medication Effect	Induction Analysis Set	Rescue Medication Effect DPS		1, 2, 4, 8, 12, 16	Exploratory
						1, 2, 4, 8, 12, 16	Exploratory
		Composite	Induction Analysis Set	Composite Maintenance DPS		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
						16, 20, 24, 28, 32, 36, 40, 44	Exploratory
Skin Pain NRS	4-point improvement	Composite	Induction Analysis Set	Composite Induction DPS: Participants with ≥4 skin pain NRS at baseline		1, 2, 4, 8, 12, 16	Exploratory
		Composite	Induction Analysis Set	Composite Maintenance DPS: Participants with ≥4 skin pain NRS at baseline		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
POEM	4-point improvement	Composite	Induction Analysis Set	Composite Induction DPS: Participants with ≥4 POEM at baseline		4, 8, 12, 16	Exploratory
		Composite	Induction Analysis Set	Composite Maintenance DPS: Participants with ≥4 POEM at baseline		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
DLQI	4-point improvement	Composite	Induction Analysis Set	Composite Induction DPS: Participants with ≥4 DLQI at baseline		4, 8, 12, 16	Exploratory

Endpoint	Variable	Estimand	Analysis Set	DPS Set	CCI	Time (Weeks) [a]	Analysis Type
		Composite	Induction Analysis Set	Composite Maintenance DPS: Participants with ≥4 DLQI at baseline		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
ADCT	5-point improvement	Composite	Induction Analysis Set	Composite Induction DPS: Participants with ≥5 ADCT at baseline		4, 8, 12, 16	Exploratory
		Composite	Induction Analysis Set	Composite Maintenance DPS: Participants with ≥5 ADCT at baseline		16, 20, 24, 28, 32, 36, 40, 44	Exploratory
ACQ-5	Change from baseline	Composite	Induction Analysis Set	Composite Induction DPS		16, 44	Exploratory
HADS	Change from baseline	Composite	Induction Analysis Set	Composite Induction DPS		16, 44	Exploratory

Abbreviations: ACQ-5 = Asthma Control Questionnaire; ADCT = atopic dermatitis control tool; CCI [redacted] DLQI = Dermatology Quality of Life Index; DPS = data points sets; EASI = Eczema Area and Severity Index; Itch NRS = Itch Numeric Rating Scale; POEM = Patient Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis; Skin Pain NRS = Skin Pain Numeric Rating Scale; vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis, HADS = Hospital Anxiety and Depression Scale.

[a] Timepoint in **bold** is the primary or secondary analysis. The non-bolded timepoints are exploratory.

6.3. Appendix C: Study Visit Mapping

As noted in Table 6.2 of the MP-SAP, Itch and Skin Pain NRS are collected as a daily diary. Table FR01.6.3 provides the mapping of diary entries for Itch and Skin Pain NRS to study visit.

[a] If date of first injection is missing, the randomization date will be used.

6.4. Appendix D: Prohibited Medication Related to AD

Prohibited medications related to AD are specified in the ISA protocol and a supplemental document will provide information on the programmatic specification of these medications.

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