Title: **An open-label single-arm study of Dupilumab in adolescent and adult skin of color patients with moderate-to-severe atopic dermatitis**

Protocol: R668-AD-2217

Compound: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

Statistician: [redacted]

Medical Director: [redacted]

Version/Date: Version 2.0 / 06DEC2024

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AD	Atopic Dermatitis
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
aOR	Adjusted Odds Ratio
BSA	Body Surface Area
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CICU	Chronic Inducible Cold Urticaria
CRF	Case Report Form (electronic or paper)
CRO	Contract Research Organization
CSU	Chronic Spontaneous Urticaria
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
EDC	Electronic Data Capture
EOSEA	End of Study Efficacy Assessment
FBR	Future Biomedical Research
FDA	US Food and Drug Administration
FST	Fitzpatrick Skin Type
GCP	Good Clinical Practice
GPS	Global Patient Safety
HADS	Hospital Anxiety and Depression Scale
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Council for Harmonization
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4Rα	IL-4 Receptor Alpha Subunit
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

Abbreviation	Term
MI	Multiple Imputation
NRS	Numerical Rating Scale
OCT	Optical Coherence Tomography
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PGID	Patient Global Impression of Disease
PHSS	Post-Inflammatory Hyperpigmentation Severity Scale
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PP	Peak Pruritus
PRO	Patient-Reported Outcome
PT	Preferred Term
QOL	Quality Of Life
Q2W	Once Every 2 Weeks
RAS	Registry Analysis Set
RBQM	Risk-Based Quality Monitoring
REAS	Registry Evaluation Analysis Set
Regeneron	Regeneron Pharmaceuticals, Inc.
RSAF	Registry Safety Analysis Set
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System Organ Class
SPNRS	Skin Pain NRS
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus and Activation-Regulated Chemokine
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroids
TEAE	Treatment-Emergent Adverse Event
TH2	Type2 Helper T cell

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of this study. The SAP is intended to be a formal and detailed description of strategy and statistical techniques to be used to realize the analysis of data for R668-AD-2217 study. Since this is an open-label single-arm study, there is no hypothesis testing to be performed. Descriptive statistics will be used to summarize efficacy and safety data from this study.

This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. These revisions will be based on review of the study and data.

1.1. Background and Rationale

Atopic dermatitis (AD), also known as atopic eczema, is a pruritic skin condition characterized by a chronic, relapsing form of skin inflammation. The pathophysiology of AD is complex and is influenced by genetic, immunologic, and environmental factors which lead to a dysfunctional skin barrier and dysregulation of the immune system. Altered epidermal barrier function, together with immune changes in the skin, lead to the development of eczematous lesions with erythema, edema, xerosis, erosions/excoriations, oozing/crusting, and lichenification that may vary by patient age, disease chronicity, as well as race and/or ethnicity.

AD usually presents during early infancy or childhood, though it can persist into or start in adulthood. The disease affects 15% to 30% of children and 2% to 10% of adults in industrialized countries, but variation related to geographic region and racial and/or ethnic origin has been described. Population-based studies in the US have demonstrated a higher prevalence of AD in African American children than in European American children. After adjusting for sociodemographic characteristics, compared to non-Hispanic whites, non-Hispanic blacks were more likely to have incident AD. Examining AD severity by self-identified racial subgroups has furthermore suggested greater severity among black children compared to white children by common outcome measures assessing AD signs and symptoms.

The clinical pattern of AD is generally heterogeneous and may additionally vary by racial subgroup. Patients of African descent are less likely to present with flexural distribution patterns but rather may present with involvement of extensor surfaces or localized disease. Furthermore, in black patients, unique primary lesional morphologies are more frequently reported including follicular AD, lichenoid AD, and papular AD. Certain secondary cutaneous changes including xerosis, lichenification, and dyspigmentation are also more common in populations comprising skin of color. Finally, a key difference in the clinical presentation of AD, relevant across skin of color AD phenotypes, relates to the distinct appearance of erythema. Specifically, where erythema is pink or red in fairly complected skin, erythema in darker skin pigmentation may be more subtle, appearing violaceous or grey or hyperpigmented (Kaufman, 2018b). Because erythema is frequently incorporated into AD scoring systems as a central indicator of inflammatory activity, disease severity in skin of color may be underestimated (Ben-Gashir, 2002). In patients with skin of color, xerosis and post-inflammatory pigment alteration are both more common and more apparent on a background of rich pigmentation, thereby adding to the burden of AD for these patients (Alexis, 2021) (Kaufman, 2018b) (Poladian, 2019).

Dupilumab is a human monoclonal antibody that targets the IL-4 receptor alpha subunit (IL-4Rα), a component of IL-4 receptors Type I and Type II, as well as the IL-13 Type II receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. As a biologic product that selectively targets the Th2 inflammatory pathway, dupilumab has demonstrated efficacy and acceptable safety for the treatment of AD in adults, adolescents, and children down to 6 months of age. The development program leading to regulatory approvals in AD consisted of global randomized controlled trials and included patients of diverse racial and ethnic background; however, non-white patients comprised less than a quarter of the enrolled population with less than 10% representing self-reported black/African American patients.

Existing data on the use of dupilumab in self-reported racial and ethnic subgroups comprising skin of color supports efficacy and safety profiles that are consistent with overall studied populations, though sample sizes are limited in the minority subgroups. Rigorous prospective characterization of AD presentations and dupilumab treatment response in a large population of skin of color patients has not been performed to date.

The primary purpose of this study is to provide additional data on the use of dupilumab in adolescent and adult skin of color patients with moderate-to-severe AD. AD presents with distinct clinical manifestations in skin of color that may contribute to diagnostic uncertainty and complicate assessment of disease activity and severity (Kaufman, 2018b). Information regarding unique clinical features and mechanisms of disease progression specifically characterizing skin of color AD as well as dupilumab treatment response will support advancement of AD management in this subpopulation with a disproportionate disease burden.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of study R668-AD-2217 is to describe further the efficacy of dupilumab on the extent and severity of eczematous lesions in skin of color participants, ≥12 years old with moderate-to-severe AD.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To describe further the efficacy of dupilumab on pruritus and other AD symptoms in skin of color participants ≥12 years old with moderate-to-severe AD
- To describe further the efficacy of dupilumab on measures of mental health (anxiety and depression) and QOL in skin of color participants ≥12 years old with moderate- to-severe AD
- To describe further the safety of dupilumab administered to skin of color participants ≥12 years old with moderate-to-severe AD
- To assess further dupilumab modulation of type 2 biomarkers in skin of color participants ≥12 years old, with moderate-to-severe AD

- To evaluate further the systemic exposure of dupilumab in skin of color participants ≥12 years old with moderate-to-severe AD

1.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To describe and photograph clinical phenotypes of moderate-to-severe AD in skin of color participants, ≥12 years old and associated dupilumab treatment responses
- To assess erythema and pigmentation changes related to moderate-to-severe AD in skin of color participants ≥12 years old through clinical assessments, patient-reported severity and impact, and direct colorimetric measurement in AD lesional, hyperpigmentation lesional, and non-lesional skin
- To assess skin dryness changes in moderate-to-severe AD in skin of color participants ≥12 years old through clinical assessment of dryness and patient-reported severity and impact
- To assess pre and post dupilumab structural changes in skin of color AD lesional, hyperpigmentation lesional, and non-lesional skin via Optical Coherence Tomography (OCT) with possible additional non-invasive imaging at the discretion of the investigator (including line field confocal OCT and/or reflectance confocal microscopy)
- To study dupilumab mechanism of action (related to efficacy and/or safety), the biology of IL-4R, IL-4, IL-13, and related pathways, AD, and related diseases.

1.2.4. Revision History for SAP Amendments

None.

2. STUDY DESIGN

2.1. Study Description and Duration

This is a phase 4 US-only multicenter open-label monotherapy study to describe further the efficacy and safety of dupilumab treatment for 24 weeks, with dosing per USPI in adolescent and adult (≥12 years old) skin of color participants with moderate-to-severe AD.

2.2. Sample Size

Due to the descriptive character of this study, no formal sample size calculation was performed. The sample size of this study was chosen empirically to support descriptive analysis of efficacy and safety in the overall skin of color population and the Fitzpatrick skin type subgroups (FST 4, 5, and 6).

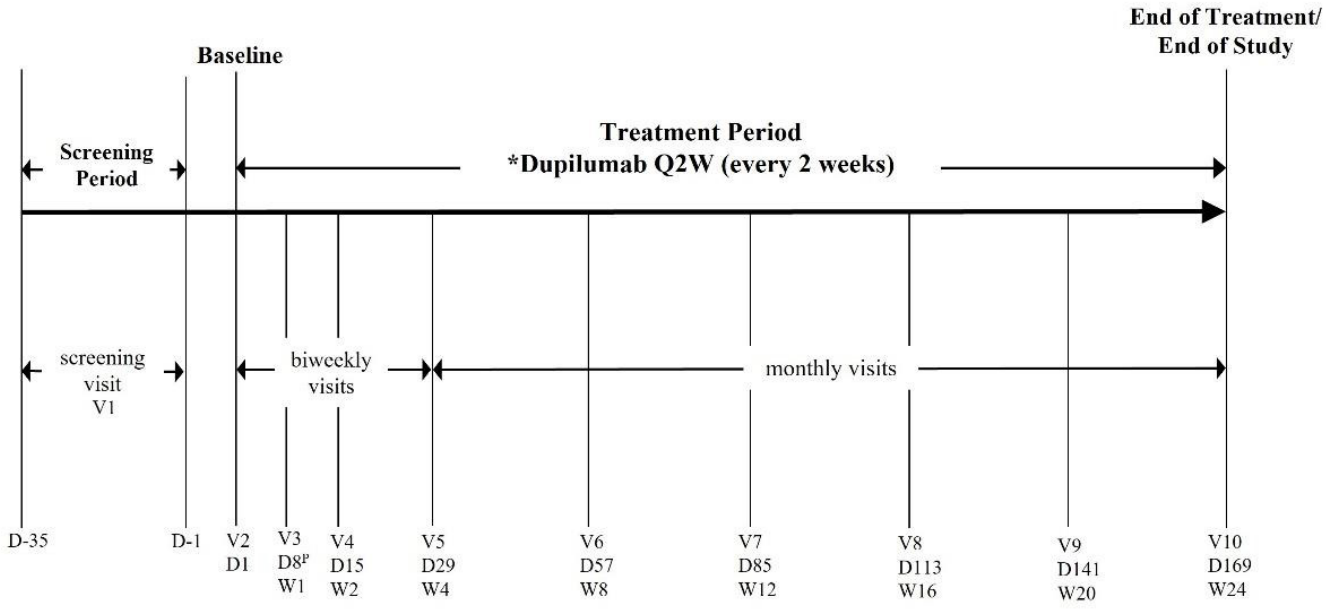
Up to 120 participants will be enrolled at approximately 30 US sites.

2.3. Study Plan

The study consists of a screening period and a treatment period.

The study flow diagram is described in Figure 1.

Figure 1: Study Flow Diagram



* Preceded by loading dose
P V3 at day 8 will be conducted as a phone visit

The Schedule of Events table is presented in Appendix 10.2.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations will be used for all statistical analyses:

3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all participants who are enrolled in the study and have baseline assessment. The FAS is the main analysis population for the study and will be used to summarize patient disposition, baseline characteristics and to analyze efficacy variables.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all participants in the FAS who are enrolled and received at least 1 dose of dupilumab during the study. Treatment administration, compliance and all safety variables will be analyzed using the SAF.

3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all participants who received any study drug and who had at least 1 non-missing PK result.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics in Study

The following demographic and baseline characteristics variables in the study will be summarized:

- Demographic variables:
  - Age (year)
  - Age group (>=12- <18 years, >=18- <40 years, >=40-<65 years, >=65 years)
  - Sex (Male, Female)
  - Standard Race Categories: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other
  - Expanded Race Categories
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Baseline Weight (kg)
  - Baseline Weight with grouping (for adolescents ages ≥ 12 to < 18 years: <60kg, ≥60kg; for adults ≥ 18 years: <60 kg, ≥60-<90 kg, ≥90 kg)
  - Baseline Height (cm)
  - BMI (kg/m^2)
  - BMI with grouping (<35, ≥35-<40, ≥40)
- Baseline characteristics:
  - Fitzpatrick Skin Type total score
  - Fitzpatrick Skin Type category
  - Duration of AD
  - Investigator's Global Assessment (IGA)
  - Eczema Area and Severity Index (EASI)
  - SCORing Atopic Dermatitis (SCORAD)
  - Body surface area (BSA) affected by AD
  - Patient Global Impression of Disease (PGID)
  - Patient Global Impression of Change (PGIC)
  - Patient Oriented Eczema Measure (POEM)
  - Dermatology Life Quality Index (DLQI) in patients ≥ 16 years of age
  - Children's Dermatology Life Quality Index (CDLQI) in patients < 16 years of age
  - Peak Pruritus Numerical Rating Scale (NRS) – weekly average at baseline

- Skin Pain NRS
- Sleep Quality NRS
- Hospital Anxiety and Depression Scale (HADS)
- AD Phenotypic Description
- Post Inflammatory Hyperpigmentation Severity Scale (PHSS)
- Dyspigmentation NRS
- Xerosis NRS

4.2. Medical History

Medical history will be coded to a Preferred Term (PT), high level term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA) at the coding CRO.

4.3. Pre-treatment / Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded to the Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken, or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures: medications taken, or procedures performed following the first dose of study drug of current study through the EOS visit.

4.4. Efficacy Data

4.4.1. Primary Efficacy Data

The primary endpoint in the study is:

EASI-75 (percent of patients achieving ≥75% reduction from baseline in EASI) at week 24

4.4.2. Secondary Efficacy Data

Secondary efficacy endpoints in this study are:

Investigator Assessed Endpoints:

- Investigator's Global Assessment (IGA)
- Eczema Area and Severity Index (EASI)

  EASI-50 (≥50% reduction from baseline in EASI)

EASI-75 (≥75% reduction from baseline in EASI)

EASI-90 (≥90% reduction from baseline in EASI)

- SCORing Atopic Dermatitis (SCORAD)
- Body surface area (BSA) affected by AD
- Post Inflammatory Hyperpigmentation Severity Scale (PHSS)
- AD Phenotypic Description

Patient Reported Outcome:

- Peak Pruritus (PP) NRS
- Sleep Quality NRS
- Skin Pain NRS
- Dermatology Life Quality Index (DLQI; age ≥16)
- Children's Dermatology Life Quality Index (CDLQI; age <16)
- Patient Oriented Eczema Measure (POEM)
- Hospital Anxiety and Depression Scale (HADS) total score, anxiety and depression sub-scores
- Patient Global Impression of Disease (PGID)
- Patient Global Impression of Change (PGIC)
- Dyspigmentation NRS
- Xerosis NRS

Detailed description of the efficacy endpoints are described in Appendix Section 10.3

4.4.3. Other Efficacy Data

Other efficacy data include:

- Photography (select sites)
- Optical Coherence Tomography and non-invasive in vivo imaging (single site)
- Colorimetry measurement sub-study (at selected sites)

4.5. Safety Data

4.5.1. Adverse Events and Serious Adverse Events Variables

Adverse events and SAEs will be collected from the time of informed consent signature and then at each visit until the end of the study. All AEs are to be coded to PT, HLT and associated SOC according to the latest available version of MedDRA at the coding CRO.

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A SAE is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or electrocardiogram (ECG) finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy

The pre-treatment period is defined as the period from the subject providing informed consent up to the first dose of study drug in current study.

The treatment period is the period starting from the first dose date up to the last dose date + 7 days.

The follow-up period is the period starting 1 day after end of treatment (EOT) period up to the EOS visit.

The overall study period consists of treatment and follow-up period.

The pre-treatment AE and TEAE are defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during pre-treatment period.
- Treatment-emergent adverse events (TEAEs) are defined as AEs with either initial onset after the first study intervention or that worsen after the first study intervention.
- Adverse event of special interest (AESI) includes these events below as listed in eCRF:

  Anaphylactic reactions

  Systemic hypersensitivity reactions

  Helminthic infections

  Any severe type of conjunctivitis or blepharitis

Keratitis

Clinically symptomatic eosinophilia

4.5.2. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.

A thorough and complete physical examination will be according to the time points in Section 10.2.

4.5.3. Laboratory Safety Variables

Pregnancy testing will be performed for all female patients of childbearing potential at time points according to Section 10.2.

4.5.4. Vital Sign Variables

N/A

4.6. Biomarker Variables

Biomarkers Endpoint for this study is:

- Change and percentage change in total and allergen-specific IgE from baseline to weeks 4, 12 and 24

Total serum IgE and allergen-specific IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgE in circulation, indicating they are atopic. To further understand atopy in this patient population, region-specific, allergen-specific IgE panels will be performed.

Samples will be collected at time points according to the schedule in Section 10.2.

5. GENERAL STATISTICAL ANALYSIS METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, Q1 (25% percentile), Q3 (75% percentile), standard deviation (SD), minimum, and maximum. For categorical or ordinal data, percentages will be displayed for each category.

5.1. Subject Disposition

The following summaries by table will be provided for all patients in FAS:

The total number of screened patients

The total number of enrolled patients

The total number of patients in each analysis set

The total number of patients who discontinued the study and the reasons for discontinuation

The total number of patients who discontinued the study treatment and the reasons for discontinuation

5.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristics as specified in Section 4.1 will be summarized for all patients in FAS.

- Demographics
- Baseline characteristics

5.3. Medical History

Medical history will be summarized by primary SOC and PT. The table will be sorted by decreasing frequency of SOC, HLT followed by PT. Medical history will be displayed on FAS.

5.4. Pre-treatment/Concomitant Medications and Procedures

Prohibited medications/procedures and rescue medications/procedures will be adjudicated from all medication/procedure collected. Number and percent of patients taking pre-treatment/concomitant medication, prohibited medications/procedures and rescue medications/procedures will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4. Patients will be counted only once for each medical class (ATC level 2 and 4) linked to the medication.

The procedure will be summarized by treatment group to the corresponding MedDRA by system organ class (SOC) and preferred term (PT) and sorted by decreasing frequency of SOC and PT.

Listing Prohibited medications/procedures and rescue medications/procedures will include generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset =defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first

dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, route.

5.5. Dose administration

N/A

5.6. Treatment Exposure and Observation Period

The duration of treatment exposure period during the study is calculated as:

(Date of last study drug injection – date of first study drug injection) + 7

Exposure will be calculated based on the last study drug injection date and first study drug injection date regardless of temporary dosing interruption.

The duration of exposure will be summarized using number of patients, mean, SD, median, minimum and maximum.

In addition, the duration of exposure will be summarized categorically by patient counts and percentages for each of the following categories and cumulatively by these categories as well:

≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days, ≥98 days, ≥112 days, ≥126 days, ≥140 days, ≥154 days.

The duration of observation period during the study in weeks is calculated as:

[(Date of the last visit – date of the first study medication dose) +1]/7.

The duration of observation period will be summarized descriptively as continues variable (n, mean, SD, median, minimum and maximum). In addition, the number and percentage of patients will be presented by specific time periods of interest as below:

≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 43 days, ≥50 days, ≥ 57 days, ≥ 64 days, ≥ 71 days, ≥ 78 days, ≥ 85 days, ≥99 days, ≥113 days, ≥127 days, ≥141 days, ≥155 days.

5.7. Analyses of Efficacy Data

The efficacy variables will be summarized for all patients in FAS. The continuous efficacy variables will be summarized using number of patients, mean, SD, median, Q1, Q3, minimum and maximum. Categorical efficacy variables will be summarized using patient counts and percentage. No formal statistical hypothesis testing will be performed. The graph of mean value for continuous variable or proportion for categorical variable by visit will be provided.

Unless otherwise specified, all observed values, regardless of whether data is collected after withdrawal from study treatment will be used for analysis.

Unless otherwise specified, for the categorical efficacy variables, the proportion of patients with each response at each visit will be calculated using the number of patients with a non-missing value at the visit as the denominator.

Subgroup analyses for efficacy

Different subgroups within the FAS population will be defined as below. The analyses will be performed for the primary efficacy variables by:

- Duration of AD (<5 years, ≥ 5years)
- Baseline weight with grouping (≥60kg, <60kg for adolescents, <60 kg, ≥60-<90 kg, ≥90 kg for adults)
- BMI with grouping (<35, ≥35-<40, ≥40)
- Age (≥12-<18, ≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Race (Black or African American, Asian, Others)
- Fitzpatrick Skin Types phototype (FST 4; FST 5 + 6 [combined])

5.7.1. Analysis of Primary Efficacy Endpoint (EASI-75)

Primary analyses:

All observed data, regardless of whether rescue treatment is used, or data is collected after study drug withdrawal, will be used to analyze the primary endpoint. Percent of patients achieving EASI-75 at week 24 will be reported. The numerator is the number of patients who achieving EASI-75 at week 24, and the denominator is the number of patients who completed assessment EASI at week 24. Patients with missing data will not be imputed as non-responders. The primary efficacy analyses will be performed on FAS.

Sensitivity analyses:

1. **Last observation carried forward – non-responder imputation (LOCF-NRI) approach:**

   For patients with missing data at week 24 who completed at least 16 weeks of treatment, missing data will be imputed by LOCF from either week 16 or week 20. Patients who received rescue therapy after week 16 will be considered non-responders.

2. **Multiple imputation (MI) approach**:

Efficacy data through week 24 after rescue medication use will be set to missing first. Missing data will be imputed by MI for 20 times based on patients who have non-missing data. The imputed week 24 EASI will determine EASI-75 response status.

Missing data from the FAS will be imputed 20 times to generate 20 complete data sets by using the SAS procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in SAS procedure MI. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates disease severity, and relevant baseline covariates.

The imputation model will include:

- The covariates included the EASI baseline value, the disease severity [IGA 3 vs IGA 4] and measured endpoint values from every clinic visit up to week 24

Week 24 data for each of the 20 complete datasets will be analyzed for EASI-75 response. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 20 analyses using Rubin's formula.

5.7.2. Analyses of Secondary Efficacy Endpoints

Statistical Analysis:

All observed data regardless of whether rescue medication is used, or data is collected after study drug withdrawal. Descriptive statistics will be provided for categorical and continuous variables. The efficacy assessment and the related analysis methods are listed below:

Assessment	Analysis Methods
EASI	• Mean and change from baseline in EASI at each visit through week 24 • Percent change from baseline in EASI at each visit through week 24 • Percent of patients with EASI-50 (≥50% reduction from baseline in EASI) at each visit through week 24 • Percent of patients with EASI-90 (≥90% reduction from baseline in EASI) at each visit through week 24
IGA	• Percent of patients with Investigator's Global Assessment (IGA) = 0 to 1 at each visit from baseline through week 24
SCORAD	• Mean and change from baseline in total SCORAD at each visit through week 24 • Percent change from baseline in total SCORAD at each visit through week 24 • Percent of patients with SCORAD-50 (≥50% reduction in SCORAD from baseline) at each visit through week 24 • Percent of patients with SCORAD-75 (≥ 75% reduction in SCORAD from baseline) at each visit through week 24 • Percent of patients with SCORAD-90 (≥ 90% reduction in SCORAD from baseline) at each visit through week 24

	• Mean and change from baseline in SCORAD Dryness component at each visit through week 24 • Percent change from baseline in SCORAD Dryness component at each visit through week 24 • Mean and change from baseline in SCORAD Erythema component at each visit through week 24 • Percent change from baseline in SCORAD Erythema component at each visit through week 24 • Mean and change from baseline in SCORAD Sleep NRS at each visit through week 24 • Percent change from baseline in SCORAD Sleep NRS at each visit through week 24 • Mean and change from baseline in SCORAD Pruritus NRS at each visit through week 24 • Percent change from baseline in SCORAD Pruritus NRS at each visit through week 24
BSA	• Mean and change from baseline in percent BSA at each visit through week 24 • Percent change from baseline in percent BSA at each visit through week 24
PHSS	• Overall Disease Severity: Mean and change from baseline at each visit through week 24 • Overall Disease Severity: Percent change from baseline at each visit through week 24 • Percent of patients in each overall disease severity grade (0-8) at each visit through week 24 • Percent of patients in each category of Pigmentary Intensity of Hyperpigmented Lesions (None, Trace, Mild, Moderate, Marked, Severe) at each visit through week 24 • Percent of patients in each Area of Hyperpigmented Lesions (None, Trace, Mild, Moderate, Marked, Severe) at each visit through week 24 • Percent of patients in each category of Degree of Hypopigmentation (None, Trace, Mild, Moderate, Marked, Severe) at each visit through week 24

	• Percent of patients in each category of Erythema, Burning, Peeling, Dryness (None, Trace, Mild, Moderate, Marked, Severe) at each visit through week 24 • In the subgroup of patients with Overall Disease Severity Score ≥ 4 at baseline: o Mean and change from baseline of Overall Disease Severity at each visit o Percent change from baseline of Overall Disease Severity at each visit o Percent of patients with decrease of ≥ 1 point at each visit o Percent of patients with decrease of ≥ 2 points at each visit o Percent of patients with decrease of ≥ 3 points at each visit o Percent of patients with decrease of ≥ 4 points at each visit o Percent of patients achieving score of 0 at each visit o Percent of patients achieving score of 0 or 1 at each visit
POEM	• Mean and change from baseline in Patient Oriented Eczema Measure (POEM) total score and item scores at each visit through week 24 • Percent change from baseline in Patient Oriented Eczema Measure (POEM) total score and item scores at each visit through week 24 • Percent of patients with ≥ 4 point Patient Oriented Eczema Measure (POEM) total score decrease from baseline at each visit through week 24
PGID	• Percent of patients in each category (None/Mild/Moderate/Severe/Very Severe) at each visit through week 24 • Percent of patients with “No Symptoms” or “Mild Symptoms” at each visit through week 24 • Percent of patients with “Moderate Symptoms” at each visit through week 24 • Percent of patients with “Severe Symptoms” or “Very severe Symptoms” at each visit through week 24
PGIC	• Percent of patients with Patient Global Impression of Change response as “Much better”, “Moderately better”,

	"A Little Better", "No Change", "A Little Worse", "Moderately Worse", "Much Worse" 7 categories at each visit through week 24
Peak Pruritus NRS	• Percent of patients with improvement (reduction) of weekly average of daily PP NRS ≥4 from baseline at each visit through week 24 • Percent of patients with ≥ 3-point improvement (reduction) of weekly average of daily PP NRS from baseline at each visit through week 24 • Mean and change from baseline in weekly average of daily PP NRS at each visit through week 24 • Percent change from baseline in weekly average of daily PP NRS at each visit through week 24
Sleep Quality NRS	• Mean and change from baseline weekly average of daily Sleep Quality NRS at each visit through week 24 • Percent Change from baseline weekly average of daily Sleep Quality NRS at each visit through week 24
Skin Pain NRS	• Mean and change from baseline in Skin Pain NRS at each visit through week 24 • Percent change from baseline in Skin Pain NRS at each visit through week 24
Dyspigmentation NRS	• Skin Lightening: mean and change from baseline at each visit through week 24 • Skin Lightening: percent change from baseline at each visit through week 24 • Percent of patients bothered by skin lightening (only in patients with non-zero skin lightening score) • Skin darkening: mean and change from baseline at each visit through week 24 • Skin darkening: percent change from baseline at each visit through week 24Percent of patients bothered by skin darkening (only in patients with non-zero skin darkening score) In the subgroup of patients who respond at baseline that they are either "very bothered (3)" or "extremely bothered (4)" by how their darkened skin looked because of AD:

	○ Skin darkening: mean and change from baseline at each visit ○ Skin darkening: percent change from baseline at each visit ○ Percent of patients in each of the following categories at each visit: • Not bothered at all (0) • Slightly bothered (1) • Somewhat bothered (2) • Very bothered (3) • Extremely bothered (4) In the subgroup of patients who respond at baseline that they are either "very bothered (3)" or "extremely bothered (4)" by how their lightened skin looked because of AD: ○ Skin Lightening: mean and change from baseline at each visit ○ Skin Lightening: percent change from baseline at each visit ○ Percent of patients in each of the following categories at each visit: • Not bothered at all (0) • Slightly bothered (1) • Somewhat bothered (2) • Very bothered (3) • Extremely bothered (4)
Xerosis NRS	• Skin dryness mean and change from baseline at each visit through week 24 • Skin dryness percent change from baseline at each visit through week 24 • Bothered by how Skin Dryness **felt:** (only in patients with non-zero skin dryness at baseline): • Not bothered at all (0) • Slightly bothered (1) • Somewhat bothered (2) • Very bothered (3)

	• Extremely bothered (4) • Bothered by how Skin Dryness **looked**: (only in patients with non-zero skin dryness at baseline) • Not bothered at all (0) • Slightly bothered (1) • Somewhat bothered (2) • Very bothered (3) • Extremely bothered (4) In the subgroup of patients who respond at baseline that they are either "very bothered (3)" or "extremely bothered (4)" by how their dry skin **felt** because of AD: o Skin dryness mean and change from baseline at each visit o Skin dryness percent change from baseline at each visit o Percent of patients in each of the following categories at each visit: • Not bothered at all (0) • Slightly bothered (1) • Somewhat bothered (2) • Very bothered (3) • Extremely bothered (4)
DLQI, CDLQI	• Mean and change from baseline in Dermatology Life Quality Index (DLQI; age ≥16) at each visit through week 24 • Percent change from baseline in Dermatology Life Quality Index (DLQI; age ≥16) at each visit through week 24 • Percent of patients with ≥4-point decrease from baseline in DLQI at each visit through week 24 • Mean and change from baseline in Children's Dermatology Life Quality Index (CDLQI; age <16) at each visit through

	week 24 • Percent change from baseline in Children's Dermatology Life Quality Index (CDLQI; age <16) at each visit through week 24 • Percent of patients with ≥4-point decrease from baseline in CDLQI at each visit through week 24
HADS	• Mean and change from baseline in Hospital Anxiety and Depression Scale (HADS) total score, anxiety and depression sub-scores at each visit through week 24 • Mean and change from baseline in Hospital Anxiety and Depression Scale (HADS) anxiety and depression sub-scores at each visit through week 24 • Percent change from baseline in Hospital Anxiety and Depression Scale (HADS) total score, anxiety and depression sub-scores at each visit through week 24 • Percent change from baseline in Hospital Anxiety and Depression Scale (HADS) anxiety and depression sub-scores at each visit through week 24 • Percent of patients s with Anxiety score < 11 among patients with baseline Anxiety score ⩾ 11 at each visit through week 24 • Percent of patients with Depression score < 11 among patients with baseline Depression score ⩾ 11 at each visit through week 24
AD phenotypic description	• Percent of each phenotype at baseline • Percent of phenotypes reported as dominant at baseline • For each dominant phenotype, anatomic distribution of lesions at baseline

5.7.3. Analyses of Other Efficacy Endpoints

The analyses of other efficacy endpoints (binary and continuous variables) will be conducted in a similar fashion as the primary analysis or secondary analysis. Imaging data and analysis will be provided by vendors.

Assessment	Analysis Method

3D Photography (select sites)	QuantifiCare will provide the methods in additional documents
Colorimetry measurement (select sites)	Lesional Target Area • Percent change from baseline to week 24 in Melanin Index • Percentage change from baseline to week 24 in Erythema Index Non-Lesional Target Area • Percentage change from baseline to week 24 in Melanin Index • Percentage change from baseline to week 24 in Erythema Index Hyperpigmented Target Area • Percent change from baseline to week 24 in Melanin Index • Percent change from baseline to week 24 in Erythema Index
Optical Coherence Tomography and non-invasive in vivo imaging (single site)	Vendor will provide the methods in additional documents

5.8. Analysis of Safety Data

The summary of safety will be performed for all patients in SAF.

5.8.1. Analysis of Adverse Events

Summaries of all TEAEs will include:

- TEAEs by primary system organ class (SOC) and preferred term (PT)
- TEAEs by Primary SOC, PT, and Maximum Severity
- Treatment-related TEAEs by Primary SOC and PT
- TEAEs Leading to Death by Primary SOC and PT

- TE-SAEs by Primary SOC and PT
- TEAEs Leading to Study intervention Discontinuation by Primary SOC and PT
- TEAEs by SOC/HLT/PT (incidence with PT ≥2%)
- AESIs by Primary SOC and PT

Listing TEAEs, serious TEAEs, severe TEAEs, TEASs leading to death and study drug discontinuation will be generated.

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5.8.2. Analysis of Clinical Laboratory Measurements

Listing of pregnancy test will be provided.

5.8.3. Analysis of Vital Signs

N/A

5.8.4. Analysis of Physical Exam

Summary of AD Phenotypic Description by percent of patients in each AD Phenotypes and dominance.

5.8.5. Analysis of Biomarker Data

Descriptive statistics for the observed values, change from baseline and percent change from baseline values by treatment and visit will be provided for the following biomarker variables:

Total serum

IgE Antigen-specific IgE

All above analyses will be performed on the FAS.

All observed data, regardless of rescue treatment is used or whether data is collected after study drug withdrawal.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the first administration of study drug in the current study. The following rules specify the determination by both date/time information:

1. For the AE, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.
2. For other data except AE, only date of the measurement will be used to determine baseline by comparing with the first injection date if date is available. If no first injection date record available, baseline visit data without available date will be used. If there is no baseline visit, screening visit data without available date will be used.

6.2. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAE. For example, if the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as "related" in the frequency tables by relation to the investigational product.

Adverse events start date

AE start date will be used for AE classification. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month,then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse events end date

The general recommendation is not to impute AE end date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If the start day is missing, and the start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If the start month is missing, and the start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to in line with the protocol which specifies to collect up to 2 years prior to medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after EOS follow-up date, use end of follow-up date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after EOS follow-up date, use the end of follow-up date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of follow-up date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in

the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

6.3. Analysis Visit Window

Data analyzed by-visit-analysis (including all efficacy data, physical exam, vital signs, biomarker) will be summarized by the study scheduled visits described in the study protocol and SAP, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, ET visits and EOT/EOS have the potential to be summarized.

The following analysis visit windows for all by-visit analysis will be used to map the unscheduled visits, ET and EOT/EOS visits, based on the study day:

visit	Targeted Study Days*	Analysis Window in Study Days
Screening	<1	<1
Baseline	1	1
Week 2	15	[2, 22]
Week 4	29	[23, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127]
Week 20	141	[128, 155]
Week 24(End of Treatment) (End of Study)	169	>=156

*study day is calculated relative to the date of first study drug injection.

In general, the following order will be used to select the record for analysis at a given visit:

3. Scheduled visit
4. Early termination (ET) or EOS, whichever comes first if scheduled visit is not available
5. Unscheduled visit if both scheduled visit and ET/EOT/EOS are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable are within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

For the daily collected ePRO data, the analysis visit windows will be implemented following the procedure below:

Step 1: Derive the study day,

- If diary date ≥ 1st injection date, then diary study day=diary date – 1st injection date +1;

- Otherwise diary study day=diary date – 1st injection date

Step 2: Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc, with 7-day intervals between visit windows.

7. INTERIM ANALYSIS

No formal interim analysis is planned for this study.

An analysis for one data snapshot is planned. The Safety analysis set (SAF) will be used for safety analyses. Week 24 completer set will be used for efficacy analyses.

Week-24 Completer Set (For Data Snapshots Prior to Database Lock)

The week 24 completer population includes all participants who have completed the week 24 study, and the patients who could have completed their week 24 assessments had they not prematurely withdrawn from the study (i.e. These patients are early dropouts, and their baseline dates are (168 + 7) days earlier than each data-cut date)

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive Statistical Method	Subgroup Analysis	Other Analyses
Continuous variables	FAS	Descriptive Statistics	No	Yes	No
Categorical variables	FAS	Descriptive Statistics	No	Yes	No

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Events

Study assessments and procedures for original global are presented by study period and visit in Table 1.

Table 1: Schedule of Events

Table 1: Schedule of Events[1]		TREATMENT PERIOD									
Study Procedure	SCNV1[2]	BL V2	Ph V3	V4	V5	V6	V7	V8	V9	ET Visit[3]	EOT / EOS V10
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
Screening/Baseline:											
Inclusion/Exclusion[4]	X	X									
Fitzpatrick skin type	X										
Informed consent/assent[5]	X										
Informed consent/assent for optional pharmacogenomics substudy[5]	X										
Informed consent/assent for optional future biomedical research substudy[5]	X										
Informed consent/assent for optional use of photographs (selected study sites only)[5]	X										
Informed consent/assent for optional colorimetry substudy (selected study sites only)[5]	X										
Informed consent/assent for optional OCT and non-invasive in vivo imaging substudy (single study site only)[5]	X										
Skin-type characterization questionnaire[6]		X									
Medical history	X										

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
POEM[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Disease[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Change[6]				X	X	X	X	X	X	X	X
Investigator Reported:											
EASI	X	X		X	X	X	X	X	X	X	X
IGA	X	X		X	X	X	X	X	X	X	X
SCORAD		X		X	X	X	X	X	X	X	X
BSA	X	X		X	X	X	X	X	X	X	X
AD phenotypic description[13]		X		X	X	X	X	X	X	X	X
Post-inflammatory hyperpigmentation severity scale (PHSS)		X		X	X	X	X	X	X	X	X
Photography (select sites)[14]		X						X		X	X
Colorimetry measurement (select sites)[15]		X		X	X	X	X	X	X	X	X
Optical Coherence Tomography and non-invasive in vivo imaging (single site)[16]		X			X			X		X	X

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
POEM[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Disease[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Change[6]				X	X	X	X	X	X	X	X
Investigator Reported:											
EASI	X	X		X	X	X	X	X	X	X	X
IGA	X	X		X	X	X	X	X	X	X	X
SCORAD		X		X	X	X	X	X	X	X	X
BSA	X	X		X	X	X	X	X	X	X	X
AD phenotypic description[13]		X		X	X	X	X	X	X	X	X
Post-inflammatory hyperpigmentation severity scale (PHSS)		X		X	X	X	X	X	X	X	X
Photography (select sites)[14]		X						X		X	X
Colorimetry measurement (select sites)[15]		X		X	X	X	X	X	X	X	X
Optical Coherence Tomography and non-invasive in vivo imaging (single site)[16]		X			X			X		X	X

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
Medication history	X										
Demographics	X										
Patient diary training[7]	X										
Treatment:											
Injection training of study drug		X									
Administer dupilumab[8,9,10]		X		X	X	X	X	X	X		
Patient diary recording dosing information		X	X	X	X	X	X	X	X		
Concomitant Medications/procedures	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[10]											
Patient Reported:											
Peak Pruritus NRS[6,11]		X (daily)									
Sleep Quality NRS[6,11]		X (daily 7 days prior to each visit)									
Skin Pain NRS[6]		X		X	X	X	X	X	X	X	X
Dyspigmentation NRS[6]		X		X	X	X	X	X	X	X	X
Xerosis NRS[6]		X		X	X	X	X	X	X	X	X
CDLQI[6,12], DLQI[6,12]		X		X	X	X	X	X	X	X	X
HADS[6]		X		X	X	X	X	X	X	X	X

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
POEM[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Disease[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Change[6]				X	X	X	X	X	X	X	X
Investigator Reported:											
EASI	X	X		X	X	X	X	X	X	X	X
IGA	X	X		X	X	X	X	X	X	X	X
SCORAD		X		X	X	X	X	X	X	X	X
BSA	X	X		X	X	X	X	X	X	X	X
AD phenotypic description[13]		X		X	X	X	X	X	X	X	X
Post-inflammatory hyperpigmentation severity scale (PHSS)		X		X	X	X	X	X	X	X	X
Photography (select sites)[14]		X						X		X	X
Colorimetry measurement (select sites)[15]		X		X	X	X	X	X	X	X	X
Optical Coherence Tomography and non-invasive in vivo imaging (single site)[16]		X			X			X		X	X

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
Safety:[10]											
Physical Examination	X									X	X
Weight / Height	X									X	X
Adverse Events[17]	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[10, 19a]											
Pregnancy Test (Urine, WOCBP only)		X		X	X	X	X	X	X	X	X
Pharmacokinetics Sampling:[18]											
Drug conc. sample[19]		X					X			X	X
Biomarkers:[19]											
Total serum IgE and allergen-specific IgEs		X			X		X			X	X
Exploratory Research Serum/Plasma		X			X		X			X	X
Future Biomarker Serum/Plasma (optional)		X			X		X			X	X
Pharmacogenomics:											
Whole blood for DNA (optional)[20]		X									

Abbreviations: BL = baseline; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; IgE = Immunoglobulin E; NRS = numerical rating scale; Ph = Phone; SCN = screening; SCORAD = SCORing Atopic Dermatitis; WOCBP = women of childbearing potential

10.3. Detailed Description of Efficacy Endpoints

Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin 2001). The EASI score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section.

EASI will be collected at the scheduled and unscheduled clinic visits as indicated in Section 10.2.

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument to rate AD disease severity globally in clinical studies. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration. IGA score will be assessed at every scheduled and unscheduled clinic visits as indicated in Section 10.2.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). The extent of AD is assessed by the Investigator as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms (erythema, oedema / papulation, excoriations, lichenification, oozing / crusts and dryness) of AD is assessed by the Investigator using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as A/5 + 7B/2 + C. The maximum SCORAD score is 103. The SCORAD will be assessed at time points as indicated in Section 10.2.

Peak Pruritus NRS (PP NRS)

The PP NRS is a simple assessment tool that participants will use to report the intensity of their pruritus (itch) during a 24-hour recall period. Participants will be asked the following question:

For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"

Participants will be instructed on using the participant diary to record their PP NRS at the screening visit. Participants will complete the rating scale daily throughout the entire study (baseline and preceding 7 days and treatment period; see Section 10.2.). Clinical sites will check and remind the participant to complete the diary according to the time points in Section 10.2..

For each day, if there are multiple NRS scores collected on the same day, the maximum value of all the scores collected will be used for analysis.

The baseline NRS is defined as the prorated average of the NRSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline NRS, the mean weekly NRS is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3.

Body Surface Area Affected by Atopic Dermatitis

The BSA affected by AD will be assessed for each major section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. Patients will undergo this assessment at baseline and subsequent study visits as indicated in Section 10.2.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire (Badia 1999) used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on Quality of Life (QoL). The format is a simple response to 10 items, which assess QoL over the past week. For each item, the scale is rated as follows: 0='not at all'='not relevant'; 1='a little'; 2='a lot'; 3='very much'='yes' in question 7, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. The DLQI will be assessed at time points according to in Section 10.2.

- Handling missing items from DLQI
  - i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
  - ii. If two or more questions are left unanswered the questionnaire is not scored.
  - iii. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
  - iv. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
  - v. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

vi. The DLQI can be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

Children's Dermatology Life Quality Index (CDLQI)

The CDLQI is a validated questionnaire designed to measure the impact of skin disease on the QOL in children ≥4 years of age (Lewis-Jones 1995). The aim of the questionnaire is to measure how much a patient's skin problem has affected the patient over a recall period of the past week. In this study, a cartoon version of the CDLQI will be administered to patients 4 to 5 years of age, with the assistance of a parent or adult "as necessary". If assistance of parent or adult caregiver is required, it is recommended that the same person assist the patient throughout the study. The cartoon version of the CDLQI uses the same text and scoring system as the original CDLQI but includes 10 color drawings of a dog illustrating the theme of each question.

To complete the questionnaire, patients need to provide responses to 10 questions (the questions focus on domains such as symptoms feelings associated with disease, the impact of the disease on leisure, school or holidays, personal relationships, sleep, and side effects of treatment for the skin disease. The instrument has a recall period of 7 days. Nine of the 10 questions are scored as follows:

- Very much = 3
- Quite a lot = 2
- Only a little = 1
- Not at all = 0
- Question unanswered = 0

Question 7 has an additional possible response (prevented school), which is assigned a score of 3. Overall scoring ranges from 0 to 30; a high score is indicative of a poor QOL. The CDLQI will be assessed at the scheduled and unscheduled clinic visits according to Section 10.2.

Handling missing items from CDLQI:

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
ii. If two or more questions are left unanswered the questionnaire is not scored.

iii. If two or more response options are ticked for one question, the response option with the highest score should be recorded.
iv. The CDLQI sub-scores may be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale will not be scored:

Sub-scales	Questions	Maximum Score
Symptoms and feelings	Questions 1,2	6
Leisure	Questions 4, 5 and 6	9
School or holidays	Question 7	3
Personal relationships	Questions 3 and 8	6
Sleep	Question 9	3
Treatment	Question 10	3

Patient Oriented Eczema Measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with atopic eczema (Charman 2004). The format is patient response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4 days', 3 = '5 to 6' days, and 4 = 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28; a high score is indicative of a poor QOL. The following POEM banding scores have been established (Charman 2004): 0 to 2 = Clear or almost clear; 3 to 7 = Mild eczema; 8 to 16 = Moderate eczema; 17 to 24 = Severe eczema; 25 to 28 = Very severe eczema. If two or more response options are selected for a question, then the response option with the highest score is recorded. If one question of the seven is left unanswered, then that question is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28. If two or more questions are left unanswered, then the questionnaire is not scored and is set to missing. If two or more response options are ticked for one question, the response option with the highest score should be recorded. Higher score indicates worse condition.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a Likert-scale tool widely used to detect states of anxiety and depression in a general hospital setting (Bjelland 2002). The 14 items on the questionnaire, assessing how the patient has been feeling in the past week, include 7 items that are related to anxiety (odd numbered questions) and 7 items that are related to depression (even numbered questions). Questions 2, 4, 7, 9, 12, and 14 are scored from 0 (less distress) to 3 (greater distress) according to the content of the item. Questions 1, 3, 5, 6, 8, 10, 11, and 13 are reverse scored from 0 (greater distress) to 3 (less distress).

A person can score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8–10 represents 'probable case' and 0–7 'not a case' (Zigmond 1983).

For each sub-scale: if one question is missing, the response will be imputed as the mean of the remaining six questions. If more than one question is missing, then the subscale is set to missing. The total score is the sum of the two sub-scores.

HADS will be assessed at time points according to Section 10.2.

Skin Pain NRS

Skin pain will be measured using a skin pain NRS that was developed and tested for the study-relevant age group. This is an 11-point scale (0 to 10) in which 0 indicates no pain while 10 indicates worst pain possible . SP NRS can be categorized as: no pain (0), mild (1 to 3), moderate (5 to 6), severe (7 to 9), and very severe (10). The threshold for minimally clinically important difference for SP NRS is between 2.2 to 2.9 (Silverberg, 2021). The SP NRS will be performed at time points according to Section 10.2.

Adult patients will be asked the following question:

- "On a scale of 0 to 10, with 0 being 'no skin pain or soreness' and 10 being 'the worst possible skin pain or soreness', how would you rate your skin pain or soreness overall, which is on average, during the past 7 days?"

Adolescent patients (≥ 12 to < 18 years at baseline) will be asked the following question:

- "Think about all the areas of your skin with eczema. How would you rate your skin pain at its worst in the past 7 days?"

Patients will be asked to complete this assessment at baseline and then approximately every month throughout the study as indicated in Section 10.2.

The baseline Skin Pain NRS score is defined as the prorated average of the Skin Pain scores reported continuously for 7 days right before the baseline visit (i.e. study day -7 to day -1). For post-baseline Skin Pain NRS score, the weekly mean of daily Skin Pain score is calculated as the average of the available reported skin pain score within the week. For example, if there are 3 scores available in a week, the prorated average = (score1 + score2 + score3)/3.

Sleep Quality NRS

Study patients will be asked to rate their sleep quality on their past night upon awakening, using the Sleep Quality NRS, ranging from 0 ("Worst possible sleep") to 10 ("Best possible sleep"). Sleep Quality NRS are to be collected daily including 7 days immediately preceding the baseline visit and then daily during the week before each planned visit.

Patients will be instructed on using the patient diary to record their Sleep Quality NRS at the screening visit. Clinical sites will check and remind the patient to complete the diary according to the time points in Section 10.2.

The baseline Sleep Quality NRS score is defined as the prorated average of the sleep quality NRS scores reported continuously for 7 days right before the baseline visit (i.e. study day -7 to day -1). For post-baseline Sleep quality NRS score, the weekly mean of daily sleep quality score is calculated as the average of the available reported daily sleep quality score within the week. For example, if there are 3 scores available in a week, the prorated average = (score1 + score2 + score3)/3.

Patient Global Impression of Disease (PGID)

The PGID is an assessment instrument used by the patient in clinical studies to rate their eczema symptoms during the past 7 days.

Patients will rate their disease based on the 5-level scale as follows:

"Overall, how would you rate your eczema symptoms during the past 7 days?"

- No symptoms
- Mild
- Moderate
- Severe
- Very severe

The PGID score will be assessed at time points according to Section 10.2

Patient Global Impression of Change (PGIC)

PGIC will be measured using a patient administered tool.

Patients will respond to the following question based on the 7-level scale as follows:

"Compared to before you started the study, how would you rate your eczema now?"

- Much better
- Moderately better
- A little better
- No change
- A little worse
- Moderately worse
- Much worse

The PGIC is an instrument used by the patient in clinical studies to compare their eczema symptoms from the beginning of the study to when they completed the assessment.

The PGIC score will be assessed at time points according to Section 10.2.

Colorimetry Measurement (Sub-study)

Colorimetry for melanin index and erythema index at AD lesional, hyperpigmentation lesional, and non-lesional targets (select sites) – At select study sites, melanin and erythema indices will be measured by handheld colorimeter probe applied to a representative area of AD (EASI erythema and papulation severity subscore each >0), a representative area of hyperpigmentation (PHSS >1 and EASI erythema and papulation severity subscore each = 0), and a representative area of background non-lesional skin (PHSS ≤1 and EASI erythema and papulation severity subscore each = 0). Efforts should be made to select photoprotected targets (to minimize confounding from UV exposure) and targets within the same anatomical region (trunk, upper extremity, lower extremity) or on the contralateral side. Subsequent measurements of the same sites will be taken at time points according to Section 10.2.

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