Clinical and Regulatory Development

Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
R668-AD-1539 PART B

Title: A PHASE 2/3 STUDY INVESTIGATING THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF DUPILUMAB IN PATIENTS AGED ≥6 MONTHS TO <6 YEARS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol: R668-AD-1539B.04

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

[redacted]

Version/Date: Version 1.0 / 28Apr2021

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.

[redacted] **(Author)**		
Print Name	Signature	Date (DDMMMYYYY)
[redacted] **(Approver)**		
Print Name	Signature	Date (DDMMMYYYY)
[redacted] **(Approver)**		
Print Name	Signature	Date (DDMMMYYYY)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of abbreviations and definition of terms

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BAS	Biomarker analysis set
BSA	Body surface area
BUN	Blood urea nitrogen
CDLQI	Children's Dermatology Life Quality Index
CGIC	Caregiver Global Impression of Change
CGID	Caregiver Global Impression of Disease
CMH	Cochran-Mantel-Haenszel
CNSQ	Caregiver-Reported Nasal Symptom Questionnaire
CRF	Case report form
DFI	Dermatitis Family Index
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
EU	European Union
FAS	Full analysis set
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonisation
IDQOL	Infants' Dermatology Quality of Life Index
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward

MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NAb	Neutralizing antibody
PASQ	Pediatric Asthma Symptom Questionnaire
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term
QW	Weekly
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SE	Standard error
SOC	System organ class
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

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 the study data. This SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to perform the analysis of data for Part B of the R668-AD-1539 study (R668-AD-1539B). Note that a separate SAP was developed and finalized for the Part A of this study (R668-AD-1539A).

This plan includes only Part B based on protocol amendment 4 and 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. This plan will be finalized prior to the database lock planned when all patients have completed end of treatment, which will be used to conduct the primary analysis of this study

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, a disturbance of the epidermal-barrier function associated with immune changes in the skin, and a high prevalence of immunoglobulin E (IgE)-mediated sensitization to food and environmental allergens.

Atopic dermatitis is one of the most common skin disorders in infants and children. The disease affects over 20% of children in many industrialized countries. A total of 45% of all cases of AD begin within the first 6 months of life, 60% begin during the first year, and 85% begin before 5 years of age.

The prevalence of AD has been estimated at a comparable 15–38% of children aged <5 years in the US (Al-Naqeeb 2019) and 21.5% of German children under age 2 (Illi 2004).

The clinical pattern of AD varies with age. Infants typically present with erythematous papules and vesicles on the cheeks, forehead, or scalp, which are exudative and intensely pruritic. The childhood phase typically occurs from 2 years of age to puberty. Children present with lichenified papules and plaques representing the more chronic disease involving the hands, feet, wrists, ankles, and antecubital and popliteal regions.

The disease has been shown to have a marked impact on the quality of life (QOL) of pediatric patients, greater than that seen in other common skin disorders like psoriasis and urticaria (Beattie 2006). A study comparing the impact on the QOL of family members of children suffering from eczema and type 1 diabetes found that all families of children with moderate-to-severe eczema had significantly higher impact scores than those of diabetic children (Su 1997).

Of particular interest in younger children is the phenomenon of “Atopic March” which is characterized by a typical sequence of progression of clinical signs of atopic disease. In general, the clinical signs of AD and of food allergies predate the development of asthma and allergic rhinitis, suggesting that AD is an “entry point” for subsequent allergic disease (Spergel 2003).

Type 2 inflammation (including Th2 responses) and the dysregulated activation of Th2 cells have been recognized as the key underlying disease drivers of AD and other associated atopic/allergic diseases. Targeting the key type 2 cytokines, IL-4 and IL-13, has the potential for treating the pathology of AD as well as other associated atopic/allergic diseases. A study was recently

conducted with the aim of identifying differences and similarities between cutaneous lymphocyte antigen (CLA) +ve, polarized T-cell subsets in children versus adults with AD. In this study, peripheral blood from children less than 5 years old was compared with that of adults with well-characterized moderate-to-severe AD, using flow cytometry. The study concluded that Th2 activation within skin-homing T cells might drive AD in children. Moreover, the spreading to additional Th subsets, particularly Th22, is seen in adults but not in children (Czarnowicki 2015).

There is currently a high unmet medical need for an effective therapy for AD with an acceptable safety profile in infants and young children who suffer with moderate-to-severe AD. Nonpharmacological management of AD, which includes environmental control measures (eg, avoidance of antigen and skin irritants) and skin care measures (eg, maintaining the hydration of the skin through the use of emollients) play a supportive role, especially in children with moderate-to-severe disease. Pharmacological management of AD in children is mainly limited to topical therapy with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). However, long-term use of TCS in children is not recommended because of the risk of irreversible skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, growth retardation, hypothalamic pituitary axis effects, etc). Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are also used in AD as an alternative to or in combination with TCS. However, both tacrolimus and pimecrolimus are not indicated for use in children <2 years of age. Moreover, the use of TCI is frequently associated with skin irritation. Furthermore, a possible increased risk of malignancy (lymphoma and skin cancers) has been noted for TCIs.

Systemic agents are used off-label in children (cyclosporine, systemic steroids, methotrexate, azathioprine, and mycophenolate mofetil). A recent survey conducted in Europe, "European Treatment of Severe Atopic Eczema in Children Taskforce (TREAT)" found that approximately 70% of respondents initiated systemic therapy for children with severe AD (Proudfoot 2013). All of these systemic agents have significant side effects in children, including stunted growth, diabetes, hypertension, and osteoporosis (corticosteroids), myelosuppression and hepatotoxicity (methotrexate), nephrotoxicity and hypertension (cyclosporine), and gastrointestinal disturbances and leucopenia (azathioprine). Moreover, a high proportion of patients in which disease is initially controlled by systemic agents suffer from relapse soon after therapy is discontinued (Schmitt 2009).

Dupilumab is a novel targeted immunoregulatory agent that selectively and simultaneously inhibits IL-4 and IL-13 signaling through the IL-4 receptor alpha subunit (IL-4Rα) by binding to the obligate shared component (IL-4Rα) of the IL-4/IL-13 receptor complex. It is intended to inhibit key disease drivers to achieve clinical benefit without the side effects commonly observed with existing non-selective systemic immunosuppressants. Dupilumab, given subcutaneously (SC), is currently in clinical trials for multiple indications, including treatment of uncontrolled severe AD in pediatric patients. Dupilumab has been approved for marketing in the US and EU for treatment of moderate to severe AD in adults and adolescents as well as for children 6-11 yrs. old with moderate to severe AD in the US, and for children 6-11 yrs. old with severe disease in the EU.

Additional detailed background information can be found in the study protocol.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of Part B of the study is to demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in pediatric patients, 6 months to less than 6 years of age, with moderate-to-severe AD.

1.2.2. Secondary Objectives

The secondary objective of Part B of the study is to assess the safety and immunogenicity of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in patients 6 months to less than 6 years of age with moderate to severe AD.

1.2.3. Modifications from the Statistical Section in the Final Protocol

The following modifications have been implemented in this SAP.

Item	Change from the Protocol	Reasons
Per protocol set (PPS) population	There will be no analysis using PPS population.	Not required by ICH.
Imputation for binary responses	Missing data due any reasons other than rescue treatment, AE, lack of efficacy (LOE) or withdrawn consent from study will be imputed by multiple imputation (MI).	Consistent with imputation method for continuous endpoints.
Imputation for continuous responses	Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AE, and lack of efficacy will be imputed by postbaseline worst-observation-carried-forward (WOCF) if there is at least one non-missing postbaseline value or by baseline value if there is no postbaseline value.	Clarify WOCF and add that missing due to withdrawn consent should be imputed by WOCF.
Onset of action analysis in percent change from baseline weekly average of daily worst scratch/itch NRS score, proportion of NRS≥3,	Add the following analysis: Onset of action in percent change from baseline weekly average of daily worst scratch/itch NRS score can be assessed by providing a nominal p-value at each assessment visits. The analysis will be carried out on the FAS population only. Using this analysis, the first assessment visit at which $p < 0.05$ for the difference from placebo in the weekly average of daily worst scratch/itch NRS score that remains $p < 0.05$ at subsequent weekly measurements through week 16	To assess the onset of effect on these endpoints.

NRS≥4, IGA 0/1, and EASI-75	can be identified. The similar analysis will be carried out on the following binary responses: • IGA 0/1 • EASI-75 • Improvement (reduction) of weekly average of daily worst itch NRS score ⩾3 from baseline • Improvement (reduction) of weekly average of daily worst itch NRS score ⩾3 from baseline	
Additional endpoint for TCS use	• Mean weekly dose of medium and/or high potency TCS through week 16	This endpoint measures the steroid sparing effect of study drug on medium or high potency TCS, which is considered to be clinically relevant.

1.2.4. Revision History for SAP Amendments

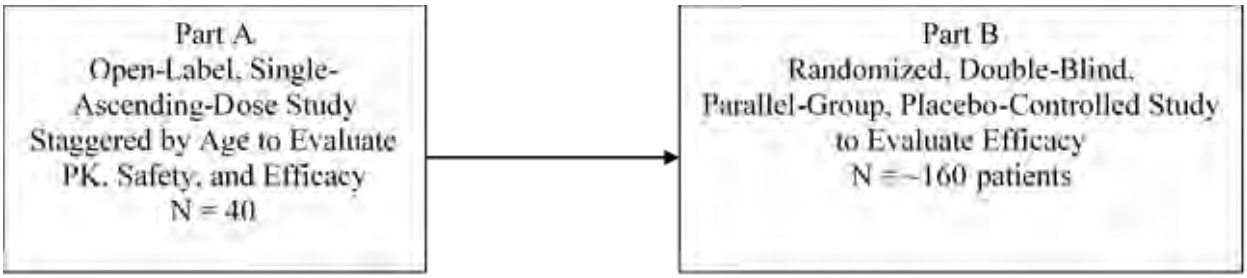
None.

2. INVESTIGATIONAL PLAN

2.1. Study Design and Randomization

The study, R668-AD-1539 is being conducted in two parts.

Figure 1: Overall Design



The Part A of AD-1539 has been completed. The CSR has been finalized and approved in Dec 2020. This document focuses on Part B of the study only.

AD-1539 B is a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of SC dupilumab when administered concomitantly with TCS in pediatric patients, ≥6 months to <6 years of age, with moderate-to-severe AD. Approximately 160 patients are planned to be randomized in the study. The number of patients with moderate AD (IGA=3) is capped at approximately 40 patients. Figure 1 shows the overall design of AD-1539 (Parts A and B).

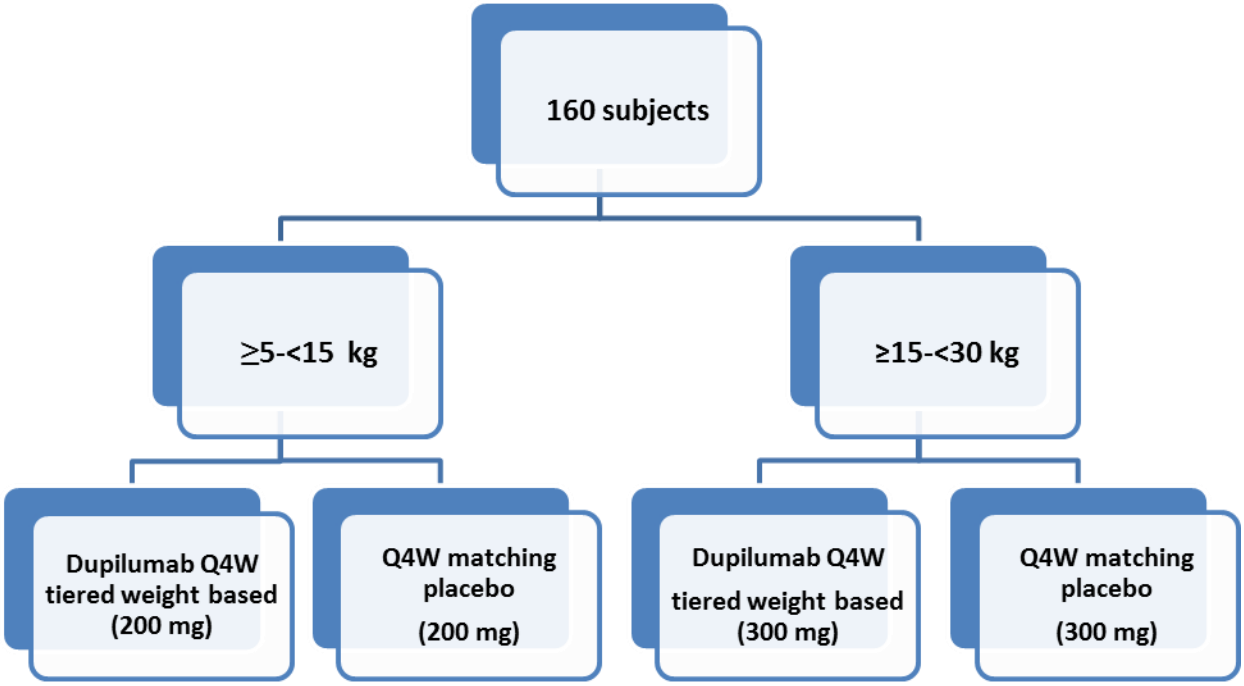
Part B consists of the following 3 periods: a screening period of up to 56 days (including 2 weeks of TCS standardization), a treatment period of 16 weeks, and a follow-up period of 12 weeks (Figure 3). Patients who enrolled in Part A of the study are not eligible to participate in Part B.

Patients who continue to meet eligibility criteria at baseline undergo day 1/baseline assessments. Patients are randomized in a 1:1 ratio stratified by baseline body weight (≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3 and 4), and region/country (North America and Europe). Approximately 160 patients are randomized to 1 of the following 2 treatment regimens (Figure 2):

- dupilumab Q4W tiered fixed-dose (200 mg or 300 mg) treatment regimen:
  - Patients with baseline weight ≥5 to <15 kg receive an SC injection of 200 mg dupilumab (1.14 mL of a 175 mg/mL solution) on day 1 and then 200 mg Q4W from week 4 to week 12.
  - Patients with baseline weight ≥15 to <30 kg receive an SC injection of 300 mg dupilumab (2 mL of a 150 mg/mL solution) on day 1 and then 300 mg Q4W from week 4 to week 12.
- placebo Q4W treatment regimen: patients receive matching placebo on day 1 and then Q4W from week 4 to week 12.
  - In the ≥5 to <15 kg weight stratum, patients randomized to placebo receive Q4W injections of placebo (1.14 mL) matching 200 mg dupilumab.

– In the ≥15 to <30 kg weight stratum, patients randomized to the placebo group receive Q4W SC injections of placebo (2 mL) matching 300 mg dupilumab.

Figure 2 Randomization Scheme for Part B



Note: Randomization will be stratified by baseline weight (≥5-<15 kg and ≥15 to <30 kg), baseline disease severity (IGA=3, 4), and region/country (North America and Europe).

2.2. Statistical Hypothesis

For the comparison of the dupilumab treatment group to placebo, the following hypotheses of the primary endpoint will be tested, where p_d is the true proportion of patients achieving IGA 0 or 1 at week 16.

Proportion of patients achieving IGA 0 or 1 at week 16

– Null hypothesis (H_0): $p_p = p_d$, i.e., the proportion of patients achieving IGA 0 or 1 at week 16 is the same between the dupilumab group and the placebo group.

– Alternative hypothesis (H_1): $p_p \neq p_d$, i.e., the proportion of patients achieving IGA 0 or 1 at week 16 is different between the dupilumab group and the placebo group.

The following co-primary endpoints (**only in the European Union [EU] and EU Reference Market Countries**) will be tested:

Proportion of patients achieving IGA 0 or 1 at week 16

– Null hypothesis (H_0): $p_p = p_d$, i.e., the proportion of patients achieving IGA 0 or 1 at week 16 is the same between the dupilumab group and the placebo group.

– Alternative hypothesis (H_1): $p_p \neq p_d$, i.e., the proportion of patients achieving IGA 0 or 1 at week 16 is different between the dupilumab group and the placebo group.

Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16

– Null hypothesis (H_0): $p'_p = p'_d$, i.e., the proportion of patients with EASI-75 at week 16 is the same between the dupilumab group and the placebo group.

– Alternative hypothesis (H1): $p'_p \neq p'_d$, i.e., the proportion of patients with EASI-75 at week 16 is different between the dupilumab group and the placebo group.

2.3. Sample Size and Power Considerations (Part B)

It is estimated that a sample size of 160 patients (80 patients per treatment group), at the 2-sided 5% significance level using Fisher's exact test, will provide the following:

- 88% power to detect a difference of 21.4% between the dupilumab and placebo groups in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 32.8% and 11.4% for the dupilumab and placebo groups, respectively.
- 99% power to detect a difference of 42.9% in the percentage of patients who achieve an EASI-75 response at week 16, assuming the percentages are 69.7% and 26.8% for the dupilumab and placebo groups, respectively.

The assumptions used for the above power calculations were based on results from patients in the R668-AD-1652 study (phase 3 combination study for patients ≥6 to <12 years of age with severe AD). The tiered fixed-dose regimen (200 mg Q4W in patients ≥5-<15 kg, 300 mg Q4W in patients ≥15-<30 kg) is expected to provided exposure comparable to that seen with 300 mg Q4W in patients ≥6 to <12 years of age or 300 mg Q2W in adult patients.

Further justification for the sample size comes from the results from the R668-AD-1224 study (a phase 3 combination [with TCS] study for adult patients with moderate-to-severe AD). In this study, the proportions of patients who achieved an IGA score of 0 to 1 at week 16 were 38.7% and 12.4% for dupilumab and placebo, respectively. The proportions of patients who achieved an EASI-75 response at week 16 were 23.3% and 68.9% for dupilumab and placebo, respectively. The study will have a power of 96% on both the co-primary endpoints based on the results from the R668-AD-1224 study. Additional support for the sample size comes from the R668-AD-1526 study (a phase 3 study for adolescent patients with moderate-to-severe AD).

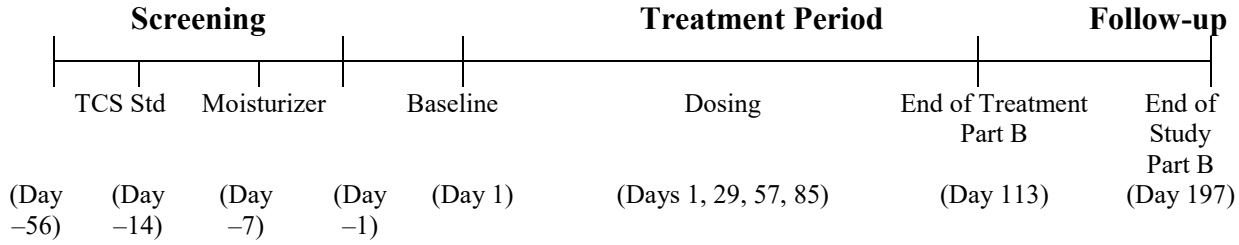
The sample size calculations were done using nQuery (7.0).

2.4. Study Plan (Part B)

The study consists of the following periods (Figure 3):

1. Screening of up to 56 days, including TCS standardization period of 2 weeks
2. Treatment period of 16 weeks, and
3. Follow-up of 12 weeks (for patients who do not enter the OLE study, R668-AD-1434)

Figure 3: Study Flow Diagram



TCS Std: topical corticosteroid standardization
Note: The length of the screening period is not fixed but must not exceed 56 days (including TCS standardization). The length of the TCS standardization period is fixed at 14 days. Moisturizers are to be applied at least twice daily during the 7 consecutive days prior to randomization (not including day of randomization) and are to be used throughout the study. At least 11 of the 14 total applications of moisturizers prior to randomization must be applied for the patient to remain eligible for the study.

Starting on day -14, all patients will be required to initiate treatment with low potency TCS using a standardized regimen (see Section 5.2 for details).

During the treatment period, patients will have in-clinic visits at baseline, week 1, week 2, and week 4, then monthly in-clinic visits through week 16 with weekly telephone visits in between the clinic visits.

Safety and laboratory assessments, samples for dupilumab concentration and ADA response to dupilumab, and efficacy assessments will be performed or collected at specified time points throughout Part B of the study according to the schedule described in study protocol. The end of treatment period visit will occur at week 16, 4 weeks after the last dose of study drug. The primary endpoint (and co-primary endpoint for EU and EU Reference Market Countries only, proportion of patients with an EASI-75, which is a key secondary endpoint for US) will be assessed at this visit.

An OLE study (R668-AD-1434) in patients aged 6 months to <18 years old is currently ongoing. Patients who complete the treatment period in Part B may subsequently be eligible to participate in the OLE study (refer to R668-AD-1434 Protocol).

Patients who decline to participate in the OLE will enter a follow-up period of 12 weeks. Follow up visits will occur every 4 weeks from week 20 through week 28. During the follow-up period, patients will be monitored for safety and tolerability and have laboratory and clinical assessments

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 of analysis will be used for all statistical analyses.

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated at randomization (as randomized). All efficacy variables will be evaluated in the FAS, which will be the primary analysis set.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive at least one dose of study drug and will be analyzed as treated. Treatment compliance/administration and all clinical safety variables will be summarized based on the SAF.

The "as treated" assignments will be made as follows:

Table 1: Assignment of "as-treated" arms

Randomized to	Treatment Received	Treatment Assignment
Dupilumab	All placebo	Placebo
Dupilumab	≥ 1 Dupilumab dose	Dupilumab
Placebo	>=1 Dupilumab dose	Dupilumab

In addition:

- Nonrandomized but treated patients will not be part of the safety population (SAF); however, their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized.

For safety summaries, three analysis periods are defined as follows:

- 16-week treatment period is defined as
  - Day 1 to the study completion date of the planned Week 16 visit (or study day 113 starting from the first dose of study drug if the date of the Week 16 treatment visit is unavailable) for those patients who completed the 16-week treatment period
  - Day 1 to the date of early termination visit, for those patients who did not complete the 16-week treatment period

- Follow-up period is defined as the date after the week 16 visit date (or study day 113 starting from the first dose of study drug if the date of Week 16 treatment visit is unavailable) to the date of the end of study visit
- Overall study Period is defined as Day 1 to the date of the end of study (EOS) visit

The SAF will be the basis for the analyses for the treatment period and overall study period; however, for the analyses for the follow-up period, only a subset of the SAF will be included, which is defined as the patients who entered the follow-up period and had at least one visit after the week 16 treatment visit (EOT).

3.3. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set includes all randomized patients who received any study drug and who had at least one non-missing drug concentration result following the first dose of study drug.

3.4. The Immunogenicity Analysis Set

The ADA analysis set (AAS) will consist of all patients who received any study drug and who had at least one non-missing ADA result after the first dose of the study drug. Patients will be analyzed according to the treatment they actually received.

The neutralizing antibody (NAb) analysis set (NAS) includes all patients who received any study drug and who tested negative at all ADA sampling times or tested positive for ADA with at least one non-missing result in the NAb assay after the first dose of the study drug; note that, patients who are ADA negative are set to negative in the NAb analysis set. Patients will be analyzed according to the treatment they actually received.

3.5. Subgroups

Subgroups are defined by key baseline factors recorded on the eCRF (unless otherwise specified) and listed as follows. The analysis for the subgroups defined may not be performed if the number of patients within the subgroup is small, e.g. <10 patients per treatment arm. No subgroup analysis will be performed if the study fails to meet its primary objective.

Subgroups to be considered for both efficacy and safety analyses:

- Age group (>6months- <2years, 2years-<6years)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black, Asian, Other)
- Duration of AD (< 3 years, ≥3 years)
- Baseline BMI (overweight: >= 85 percentile of BMI for >=2 years based on age and gender, >= 95 percentile of weight based on length (height), age and gender for < 2 years, Not overweight: not meeting the criteria of overweight) [based on CDC (Center for Disease control and Prevention) chart]

- Baseline weight group (>=5- <15kg, >=15-<30kg)

Subgroups listed for primary and key secondary efficacy endpoints:

- Age of disease onset (<2 years, ⩾2years)
- Family history of atopic disease (Yes/No)
- Region (North America, Europe)
- Baseline EASI (<25, >=25)
- Baseline worst scratch/itch scale (<7, ⩾7)
- Body Surface Area (BSA) (≥10%-<30%, ≥30%-<50%, ≥50%)
- Baseline SCORAD score (<50, ≥50)
- Previous usage of ciclosporin (CsA) (Yes, No)
- Previous use of systemic immunosuppressants (Systemic Corticosteroid and Systemic Non-Steroidal Immunosuppressant) for AD (Yes, No)
- History of asthma (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergies (Yes, No)

In addition, for analysis of conjunctivitis TEAEs, sub-group analysis based on medical history of conjunctivitis (yes/no) may be performed. TEAE and overall AE summary will be provided by history of food allergies subgroup.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Demographic variables: Age at screening (year), Age group (>6m-<2Y, 2Y-<6Y), Sex (Male, Female), Ethnicity (Hispanic or Latino, Not-Hispanic or Latino), Race (White, Black or African American, Asian, Other), Region (North America, EU), Baseline weight (kg), Baseline weight with grouping (>5-15 kg, >15-30 kg), height (m), BMI [for >= 2 years, BMI will use weight/ height^2 formula; for <2 yrs., BMI will use weight for length formula (weight/length)], BMI with grouping (overweight, not overweight) [using the separate formula by age as described previously]
- Baseline characteristics: Duration of AD disease with grouping (< 3 years, >=3 years), worst scratch/itch NRS score, Investigator's Global Assessment (IGA) score [IGA = 3, 4], Eczema Area and Severity Index (EASI) score, SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) affected by Atopic Dermatitis, Caregiver global impression of disease (CGID), Patient Oriented Eczema Measure (POEM), Children's Dermatology Life Quality Index (CDLQI for patients >=4 years of age), Infants' Dermatology Quality of Life Index (IDQOL for patients <4 years of age), Global Individual Signs score (GISS), Dermatitis Family Index (DFI), NRS Skin Pain, NRS Sleep, Patients with inadequate response to topicals (Yes/No), Pediatric Asthma Symptom Questionnaire (PASQ, only for patients with ongoing asthma), Caregiver-Reported Nasal Symptom Questionnaire (CNSQ, only for patients with allergic rhinitis)

4.2. Medical History and Atopic Disease Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Information on conditions related to AD including diagnosis of AD and AD treatment history, personal and/or family history of asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy, hives and other allergies due to medications, animals, plants, mold, dust mites, etc. are collected. Recent AD topical treatments history within 6 months before the screening visit is also collected. History of treatment with systemic immunosuppressants for AD (cyclosporine, systemic corticosteroids, methotrexate, azathioprine and other treatments) during the last 6 months will also be collected.

4.3. Prior / 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 using WHO Drug Dictionary (WHODD). If a patient takes more than one medication within the same medication class, this patient will be counted only once in the summary. Procedures will be coded using MedDRA.

Prior medications/procedures: medications taken, or procedures performed prior to administration of the first dose of study drug.

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

- Concomitant medications/procedures during the 16-week treatment period are medications/procedures taken after the first dose up to the week 16 visit date or date of study day 113 if the week 16 visit date is missing. Medications/procedures taken during the 16-week treatment period and continued afterwards into the follow-up period will be counted only once as concomitant medications/procedures during the 16 week treatment period.
- Concomitant medications/procedures during the follow-up period are medications/procedures taken after the week 16 visit date to end of study.

Prohibited concomitant medications/procedures: Treatment with the following **concomitant medications** is prohibited during the study:

- Treatment with a live (attenuated) vaccine (e.g. Chickenpox (Varicella), Mumps)
- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating biologics
- Treatment with systemic nonsteroidal immunosuppressant (e.g. cyclosporine, methotrexate) [may be used as rescue]
- Treatment with crisabarole (may be used as rescue)
- Treatment with medium potency, high-potency or very high potency TCS, (medium or high potency TCS may be used as rescue)
- Treatment with TCI (may be used as rescue) [Note: The use of TCI is prohibited during the 2-week screening period leading up to the baseline visit, and the treatment and follow-up periods]
- Initiation of treatment of AD with prescription moisturizers

The following **concomitant procedures** are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy (ultraviolet A and/or ultraviolet B)

For details of permitted and prohibited medications, see Appendix 1.

Rescue treatments (i.e. both medications and procedures):

If medically necessary (i.e. to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. The use of rescue treatment is only allowed after day 14 of the study. Investigators will be required to perform an IGA assessment prior to starting rescue treatment and initiate rescue treatment only in patients who either have an IGA score >= 3 or have intolerable symptoms. If possible, investigators are encouraged to consider

rescue initially with topical treatment (e.g., high potency TCS) and to escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. Patients may continue study treatment if rescue consists of topical medications. Patients who receive systemic corticosteroids or systemic non-steroidal immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) as rescue medication during the study will be discontinued permanently from the study drug. All patients will be asked to complete the scheduled study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (e.g., disease severity scores, safety laboratory tests) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary. For the purpose of efficacy analysis, patients who receive rescue treatment during the study will be considered treatment failures.

For the purpose of the efficacy responder analysis, a pre-specified algorithm will be used to classify rescue (details in Section 5.6.1). In addition, a blinded review of all post-baseline medications to adjudicate rescue treatment, based on medical judgement, will be performed to adjudicate rescue. Patients who receive rescue treatment as per this adjudication during the study will be considered as treatment failures.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variable

The primary endpoint in the study is:

- Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16

For the **EU and EU Reference Market Countries only**, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16

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 the scheduled and unscheduled clinic visits according to Appendix 3 .

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 as follows: the head and neck (H), upper extremities (U), trunk (T), and lower extremities (L) are assigned proportionate body surface areas of 20% (H), 20% (U), 30% (T), and 30% (L), roughly consistent with the 'rule of nines". 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.

The EASI will be collected at the scheduled and unscheduled clinic visits according to Appendix 3.

4.4.2. Secondary Efficacy Variables

The key secondary endpoints:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (**not applicable for EU or EU Reference Market Countries**)
- Percent change in EASI score from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score

Pruritus (worst scratch/itch) NRS score

Itch will be measured using a worst scratch/itch 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 scratching/itching while 10 indicates worst scratching/itching possible. The parents/caregivers will be asked to:

"Answer the question below based on what you observe and what your child tells you (if applicable):"

"How would you rate your child's scratching/itching at its worst in the past 24 hours?"

Pruritus will be assessed by the parent/caregiver on a daily basis using an e-diary throughout the entire study (i.e., screening, treatment, and follow-up periods).

Parents/caregivers will be instructed on using the scale to record their child's pruritus score at the screening visit. Using the e-diary, parents/caregivers will complete the rating scale DAILY through the entire study (screening, treatment, and follow-up periods). Clinical sites will check parent/caregiver data, collected using the e-diary, for protocol compliance and remind parents/caregivers to complete the e-diary throughout the study.

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

Other secondary efficacy endpoints:

- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Change from baseline to week 16 in percent BSA affected by AD
- Percent change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score
- Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline at week 16
- Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline to week 16
- Change from baseline to week 16 in skin pain NRS
- Change from baseline to week 16 in patient's sleep quality NRS
- Change from baseline to week 16 in caregiver's sleep quality NRS
- Change from baseline to week 16 in health-related quality of life, as measured by CDLQI score (patients ≥4 years of age)
- Change from baseline to week 16 in health-related quality of life, as measured by IDQOL score (patients <4 years of age)
- Change from baseline to week 16 in Dermatitis Family Index, DFI score
- Change from baseline to week 16 in POEM score
- Topical treatment for AD – proportion of TCS medication-free days from baseline to week 16
- Mean weekly dose of low potency TCS through week 16
- Mean of caregiver missed workdays (CMW) from baseline to week 16

Secondary endpoints for safety:

- Incidence of skin infection TEAEs (excluding herpetic infections) through week 16*
- Incidence of SAEs through week 16

**Adjudicated by study medical director.*

Additional secondary efficacy endpoints (that are not in protocol):

- Mean weekly dose of medium or high potency TCS through week 16

Skin Pain NRS

Skin pain will be assessed by the parent/caregiver at time points during Part B according to Appendix 3. Skin pain will be measured during Part B 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. The parents/caregivers will be asked to:

"Think about all the areas of your child's skin with eczema. Answer the question below based on what you observe and what your child tells you (if applicable)."

"How would you rate your child's skin pain at its worst in the past 24 hours?"

Clinical sites will check and remind the parent/caregiver to complete the scale according to the time points in Appendix 3. Parents/caregivers will be instructed on using the scale to record their child's skin pain score at the screening visit. Parents/caregivers will complete the rating scale DAILY for the 14 days prior to the baseline visit, for the 7 days prior to the week 2 visit, for the 7 days prior to the week 4 visit, for the 7 days prior to the week 16 visit, and for the 7 days prior to the week 28 visit. Clinical sites will check parent/caregiver data collected using an e-diary for protocol compliance and remind parents/caregivers to complete their e-diary throughout the study. Higher score indicates worse condition.

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

A sleep diary will be completed by the parent/caregiver at time points during Part B according to Appendix 3. The sleep diary includes 2 questions assessing the caregiver's sleep, and 6 questions assessing the child's sleep based on caregiver observation. Sleep diary items, either alone or in combination will serve as subjective measures of sleep quality, difficulty falling asleep, nighttime awakenings, and sleep duration. Sleep quality will be measured using an 11-point NRS (0 to 10) in which 0 indicates worst possible sleep while 10 indicates best possible sleep. The parents/caregivers will be instructed to complete the questions about the child's sleep upon awakening for the day as well as to complete the questions about their own sleep.

Clinical sites will check and remind the parent/caregiver to complete the diary according to the time points in Appendix 3. Parents/caregivers will be instructed on using the diary to record their child's sleep quality score at the screening visit. Parents/caregivers will complete the diary DAILY for the 14 days prior to the baseline visit, for the 7 days prior to the week 1 visit, for the 7 days prior to the week 2 visit, for the 7 days prior to the week 4 visit, for the 7 days prior to the week 16 visit, and for the 7 days prior to the week 28 visit. Clinical sites will check parent/caregiver data collected using an e-diary for protocol compliance and remind parents/caregivers to complete their e-diary throughout the study. Higher score indicates better condition.

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.

Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (head, trunk, arms, and legs) and will be reported as a percentage of all major body sections combined. The possible highest score for each region is:

Age	Head	Torso	Lower Extremities	Upper Extremities	Genitals
6 months - <2 years	18%	36%	28%	18%	0%
2 - <3 years	17%	36%	29%	18%	0%
3 - <4 years	16%	36%	30%	18%	0%
4 - <5 years	15%	36%	31%	18%	0%
5 - < 6 years	14%	36%	32%	18%	0%

Total BSA will be the sum of all individual body areas. Patients will undergo this assessment at the scheduled and unscheduled clinic visits according to Appendix 3.

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 objective SCORAD is calculated as A/5 + 7B/2. The maximum objective SCORAD score is 83. Higher score indicates worse condition.

Patients will undergo this assessment at the scheduled and unscheduled clinic visits according to Appendix 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 Appendix 3.

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

Infants' Dermatology Quality of Life Index (IDQOL)

The IDQOL is a validated questionnaire developed to measure the impact of skin disease on the QOL of infants and preschool children <4 years of age (Lewis-Jones 2001). The IDQOL is to be completed by the child's parent or caregiver. It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study. The questionnaire consists of 10 questions related to itching and scratching; mood of the child; how long it takes for the child to get to sleep; whether the eczema has interfered with the child's playing, swimming or participation in other family activities; problems during mealtimes; problems caused by treatment; level of comfort while dressing or undressing the child; and problems during bathing. Each question asks about the impact over the previous week and is scored on a scale of 0 (minimum impact) to 3 (maximum impact). A high score is indicative of a poor QOL

The IDQOL for a patient is the sum of the score of each question with a maximum of 30 and a minimum of 0. The higher the score, the greater the impact is on the QOL. The IDQOL can also be expressed as a percentage of the maximum possible score of 30. Handling missing items from IDQOL will be same as that of CDLQI. The IDQOL sub-scores may be analyzed by calculating the score for each of its sub-scales, as appropriate. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale will not be scored.

This assessment will be performed in Part B at time points according to Appendix 3.

Sub-scales	Questions	Maximum Score
Symptoms (1 item)	Question 1	3
Difficulties with mood (1 item)	Question 2	3
Sleep (2 items)	Questions 3, 4	6
Play (1 item)	Question 5	3
Family activities (1 item)	Question 6	3

Mealtimes (1 item)	Question 7	3
Treatments (1 item)	Question 8	3
Dressing (1 item)	Question 9	3
Bathing (1 item)	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.

This questionnaire asks the caregiver to report their perception of the patient's AD symptoms. It is therefore completed by the caregiver. It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study.

Caregiver Assessment of Missed Workdays (CMW)

Caregivers who are employed will be asked to report the number of sick-leave days since the last study assessment. Caregivers will undergo this assessment at the time points according to Appendix 3.

Dermatitis Family Index (DFI)

The impact on family life has been documented in families of children with very severe AD. The DFI was the first instrument assessing the impact of having a child with AD on family QOL (Lawson 1998). The 10-item disease specific questionnaire was formed after ethnographical interviews and focus groups revealed the areas of family QOL affected by AD. The self-administered instrument is completed by an adult family member of a child affected by dermatitis. The items inquire about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships and the impact of helping with treatment on the primary caregiver's life. The DFI questions are scored on a four-point Likert scale ranging from 0 to 3, so that the total DFI score, which is calculated as sum of all 10 questions,

ranges from 0 to 30. The time frame of reference is the past week. A higher DFI score indicates greater impairment in family QOL as affected by AD. The DFI will be assessed at time points according to Appendix 3. Note that, DFI is also called as Dermatitis Family Impact.

Handling missing items from DFI:

v. 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.
vi. If two or more questions are left unanswered the questionnaire is not scored.
vii. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

4.4.3. Exploratory Efficacy Variable(s)

Exploratory efficacy endpoints include:

- Proportion of patients with SCORAD-50 (>=50% reduction in SCORAD from baseline) response at week 16
- Proportion of patients with SCORAD-75 (>=75% reduction in SCORAD from baseline) response at week 16
- Proportion of patients with SCORAD-90 (>=90% reduction in SCORAD from baseline) response at week 16
- Caregiver global impression of disease (CGID):
  - Proportion of patients with No symptoms at week 16
  - Proportion of patients with No symptoms or Mild symptoms at week 16
- Caregiver global impression of change (CGIC):
  - Proportion of patients who rate their eczema symptoms as “Much better” at week 16
  - Proportion of patients who rate “Much better” or “Moderately better” at week 16
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve an IGA score of 2 (mild disease) or less at week 16
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Proportion of patients with IGA score 0 or 1 or EASI-90 at week 16
- Change from baseline in PASQ score at week 16 (for patients with Asthma)
- Change from baseline in CNSQ score at week 16 (for patients with medical history of allergic rhinitis)

Caregiver Global Impression of Disease (CGID)

The CGID is an assessment instrument used by the parent/caregiver in clinical studies to rate their child's eczema symptoms during the past 7 days. An appropriate version of the CGID was being developed and tested for the study-relevant age group.

Parents/caregivers will rate their child's disease based on the 5-level scale as follows:

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

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

The CGID score will be assessed at time points according to Appendix 3.

Caregiver Global Impression of Change (CGIC)

Caregiver global impression of change will be measured using a caregiver administered tool that is currently being developed and tested for the study-relevant age group.

Parents/caregivers will respond to the following question based on the 7-level scale as follows:

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

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

The CGIC is an instrument used by the parent/caregiver in clinical studies to compare their child's eczema symptoms from the beginning of the study to when they completed the assessment.

The CGIC score will be assessed at time points according to Appendix 3.

Global Individual Signs Score (GISS)

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally by the Investigator (i.e., each assessed for the whole body, not by anatomical region) on a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe) using the EASI severity grading criteria. The cumulative score is the sum of the four components, which

will be ranged from 0 to 12. A higher GISS score indicates worse AD lesions of the patient. Handling missing items from GISS:

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 12.
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.

The GISS will be assessed at the scheduled and unscheduled clinic visits according to Appendix 3.

Pediatric Asthma Symptom Questionnaire (PASQ)

The PASQ is a questionnaire developed by the sponsor to monitor asthma control in preschool children in clinical trial settings. The advantage of the PASQ is the much shorter recall period for various items to fit the schedule of clinical trials and improvement in ability to recall as compared to existing instruments. The questionnaire consists of 6 questions related to asthma control.

The questionnaire will be completed only for the subset of patients with ongoing asthma. It is to be completed by the child's parent or caregiver who fluently speaks a language in which the questionnaire is presented, at time points according to Appendix 3. It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study. Questions 4, 5, and 6 will only be answered if the answer to Question 3 is > 0 days. Higher score indicates worse condition (asthma severity).

The following algorithm will be implemented to calculate PASQ score.

- Questions 1 & 2 should still be calculated and summarized separately.
- For questions 3 to 6 (ranged from 0 to 4), total score, which can be termed as PASQ score. will be calculated.
  - If answer to question 3 is 0, then the total score is 0, regardless of answers to questions 4-6;
  - If answer to question 3 is non-zero and answers to questions 4 to 6 are all 0, then the total score will be equal to the score for question 3;
  - If answer to question 3 is non-zero and answers to questions 4 to 6 are also non-zero values, then the total score is calculated by adding the scores for questions 4 to 6; Also ignore the score in question 3.

Handling missing items from PASQ:

If answer to question 3 is missing and answers to questions 4-6 are non-missing, then the total score is calculated by adding the scores for questions 4 to 6; if one item from questions 4 to 6 is missing, set the score of the missing item as the average of the other two non-missing items from questions 4-6 and calculate total score. If two or more items from questions 4-6 are missing, then set the total score as missing.

If answer to question 3 is non-missing and non-zero, and if one item from questions 4-6 is missing, set the score for the missing item as the average of the other two non-missing items from questions 4-6 and calculate total score. If two or more items from questions 4-6 are missing, then set the total score as missing.

Caregiver-Reported Nasal Symptom Questionnaire (CNSQ):

The CNSQ will be used to assess the effect of study drug on symptoms of allergic rhinitis. The summed score will include the following 4 symptoms: runny nose, nasal congestion, nasal itching, and sneezing, each rated on a 0 to 3 scale of severity. The questionnaire will be completed only for the subset of patients with a medical history of allergic rhinitis. It is to be completed by the child's parent or caregiver who fluently speaks a language in which the questionnaire is presented (based on availability of translations in participating countries). Total score is the sum of all symptom scores. If there is one symptom score missing, the total score is set to missing. The minimum and maximum possible values of the total CNSQ score are 0 and 12. Higher score indicates worse condition.

Caregivers will be instructed on using the e-diary to record the CNSQ during the screening period (for the 14 days before baseline/day 1) and for the 7 days preceding visits for weeks 4, 16, and 28 as described in Appendix 3.

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

4.5. Safety Variables

4.5.1. Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events (SAE) will be collected starting from the time of informed consent signature and at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term (PT)", "High Level Term (HLT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA).

The criteria for determining whether an abnormal laboratory, vital sign or 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 patient providing informed consent up to the first dose of study drug. The treatment and follow-up period is defined as the period from the administration of first study dose to the EOS visit.

Pre-treatment AEs and treatment emergent AEs (TEAEs) are defined as follows:

- Pre-treatment AEs are AEs that developed or worsened in severity during the pre-treatment period.

- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered TEAEs.
- TEAEs during the 16 week treatment period are AEs with onset after the first dose up to the week 16 visit date (study day 113 if the week 16 visit date is missing) or early termination visit, whichever is earlier. TEAEs that have an onset during the 16 week treatment period and continued afterwards into the follow-up period will be counted only once as TEAEs during the 16 week treatment period.
- TEAEs during the follow-up period are AEs with onset after the week 16 visit date up to the end of the study.

AEs of Special Interest (AESI):

The following AESIs will be analyzed:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

Other AEs:

Skin Infections (with adjudication by clinical), Herpes Infections and Injection Site Reactions will be analyzed.

Additionally other AEs such as Narrow and Broad Conjunctivitis CMQ will be analyzed.

- **Narrow conjunctivitis** CMQ is defined as the following PT terms
  - Conjunctivitis
  - Conjunctivitis allergic
  - Conjunctivitis bacterial
  - Conjunctivitis viral
  - Atopic Keratoconjunctivitis
- **Broad conjunctivitis** CMQ is defined as the following PT terms
  - Conjunctivitis
  - Conjunctivitis allergic
  - Conjunctivitis bacterial
  - Conjunctivitis viral

- Atopic Keratoconjunctivitis
- Blepharitis
- Dry eye
- Eye irritation
- Eye pruritus
- Lacrimation increased
- Eye discharge
- Foreign body sensation in eyes
- Photophobia
- Ocular hyperaemia
- Conjunctival hyperaemia
- Xerophthalmia

Note that, Appendix 4 provides a list of AESIs search criteria.

4.5.2. Laboratory Safety Variables

Hematology, and chemistry samples will be analyzed by a central laboratory.

Samples for laboratory testing will be collected according to visit schedule (Appendix 3). Tests will include

Serum Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol[2]
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	AST	Uric acid
Calcium	ALT	CPK[3]
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

1 Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN
2 Low-density lipoprotein and high-density lipoprotein
3 CPK isoenzymes will be measured when CPK >5× the ULN

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Other Laboratory Tests

The following tests will be performed at screening: HIV, HBsAg, HBsAb, HBcAb, hepatitis C antibody, tuberculosis (will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards). Serum samples for vaccination response will be collected at time points as described in Appendix 3.

4.5.3. Vital Sign Variables

The following vital signs parameters will be collected:

- Respiratory rate (bpm)
- Heart rate (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (^{o}C)

Patients will be monitored at the study site at certain dosing visits for a minimum of 2 hours after study drug administration. Vital signs (systolic and diastolic blood pressure, heart rate, respiration, and temperature) will be performed at 30 minutes (±10 minutes) and 2 hours (±15 minutes) post-injection. See Appendix 3 for assessment time points.

4.5.4. Body Weight and Height

Body weight and height will be measured at time points according to Appendix 3.

4.5.5. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal. A thorough and complete physical examination will be performed at time points according to the schedule described in Appendix 3.

4.5.6. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] =QT/[$RR^{0.33}$]) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. See Appendix 3 for assessment time points.

4.6. Pharmacokinetic (PK) Variables

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Appendix 3. PK parameters may include, but are not limited to C_{trough} and $C_{trough,SS}$.

4.7. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status and time-point/visit. Serum samples for anti-dupilumab antibody testing will be collected at time points according to the visit schedule described in Appendix 3. Samples positive in the ADA assay will be analyzed for the presence of neutralizing antibody in the NAb assay.

- ADA Negative, defined as ADA negative response in the dupilumab ADA assay at all timepoints, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the dupilumab ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 4-fold of baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the dupilumab ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses may be further characterized as Persistent, Indeterminate or Transient.
- Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 12-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
- Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
- Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the dupilumab ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Maximum Titer categories (Maximum titer values) are provided below.

Low (titer <1,000)
Moderate (1,000 ≤ titer ≤ 10,000)
High (titer >10,000)

4.8. Biomarkers Variables

Biomarkers to be analyzed in this study are:

- TARC
- Total serum IgE
- Immunoglobulin profiling
- Antigen-specific IgE
- Lactate dehydrogenase (LDH) [which will be measured as part of the blood chemistry]

Serum samples for measurements of biomarkers to study the PD activity of dupilumab in pediatric AD patients will be collected at time points according to Appendix 3.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, first quartile (Q1), third quartile (Q3), minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

All data will be summarized by 2 treatment groups (i.e., dupilumab 200/300 mg Q4W and placebo).

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for the FAS.

5.2. Medical and AD History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC, followed by PT, based on the overall incidence across treatment groups. Medical history will be listed, sorted by treatment groups.

Information on conditions related to AD will be summarized and includes diagnosis of AD and AD treatment history, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy hives and other allergies due to medications, animals, plants, mold, dust mites, etc..

All analyses will be based on the SAF population.

5.3. Prior/Concomitant Medications/Procedures

The number and proportion of patients taking prior/concomitant medications, prohibited medications and rescue medications will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined dupilumab treatment group. Patients will be counted only once for each medication class (ATC level 2 and 4) linked to the medication.

The number and proportion of patients taking prior/concomitant procedures, prohibited procedures and rescue procedures will be summarized, sorted by decreasing frequency of SOC and PT based on the overall incidence for the dupilumab treatment group. Patients will be counted only once for each SOC and PT linked to the procedure.

The number and proportion of patients taking adjudicated rescue treatment (concomitant topical treatments (medium to high potency TCS/TCI), systemic immunosuppressants) and/or other treatments (emollients/ antihistamines) will also be summarized separately.

The compliance with protocol requirements for application of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group

In addition, the summary of prior/concomitant medications/procedures may be provided for subjects who were impacted by the COVID-19 pandemic and not impacted by COVID-19 pandemic in each study period. The summary will be performed for pre-, during, and post-COVID-19 periods for subjects impacted by COVID-19, if deemed appropriate. The COVID-19 periods are consisting of 'Pre COVID-19 period', 'Post COVID-19 period' and 'During COVID-19 period' using start date and end date of being affected by COVID-19 for each patient who are affected by COVID-19.

Kaplan Meier curves for time to first rescue use will be generated.

5.4. Subject Disposition

The following summaries will be provided for each treatment group and study total (unless otherwise specified):

- The total number of screened patients who signed ICF, along with reasons for screen failure (for study total only)
- The total number of randomized patients (patients who received a randomization number)
- The total number of patients in each analysis set
- The total number of patients who completed the study and discontinued the study with the reason of discontinuation (including COVID-19 related reasons)
- The total number of patients who completed the study treatment and discontinued the study treatment with the reason of discontinuation (including COVID-19 related reasons)
- The total number of patients who continued on to the pediatric open label extension study
- The total number of patients who entered into the follow-up period and their study completion status, with reason of discontinuation (including COVID-19 related reasons), if applicable

5.5. Extent of Study Treatment Exposure and Compliance

5.5.1. Measurement of Compliance

The compliance with protocol-defined study drug administration will be calculated as follows:

Treatment Compliance= (Number of study drug injections during exposure period) / (Number of planned study drug injections during exposure period) x 100%

The summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

5.5.2. Exposure to Study Drug and Observation Period

The duration of treatment (Q4W dosing) exposure during the study in day is calculated as:

(Date of last study drug injection – date of first study drug injection) + 28 days

The calculations do not take into account temporary dosing interruption including due to COVID-19. The summary of exposure to study drug will include the number of study drug doses administered and the duration of exposure. Duration of exposure will be summarized for each treatment group using the number of patients, mean, SD, minimum, median, Q1, Q3, and maximum.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories cumulatively by these categories: ≥ 28 days, ≥ 56 days, ≥ 84 days, and ≥ 112 days with an increment of 4 weeks for each subsequent category.

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

(Date of the last visit – date of the first study drug injection) +1.

The duration of observation period will be summarized descriptively using number of patients, mean, SD, median, Q1, Q3, minimum and maximum. In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest are specified as:

< 8 days, ≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥113 days, ≥141 days, ≥169 days, and ≥197 days.

5.6. Analyses of Efficacy Variables

The analyses of efficacy variables are described in the subsections below and summarized in Appendix 2. The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimands of interest for the co-primary endpoints (**only in European Union [EU] and EU Reference Market Countries**) and key secondary endpoints are provided below.

	Estimands			
Endpoint Category	**Endpoints**	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary/Analysis Method**
Co-primary (Proportion)	• Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16 • Proportion of patients with EASI-75 at week 16	FAS	The intercurrent events will be handled as follows: • Discontinuation of study intervention: Data collected after the patient discontinued treatment will be included in the analyses (treatment policy strategy). • Initiation of rescue treatment: Patients will be considered as non-responders after such events (composite strategy). Missing data imputation rules: • Missing data due to withdrawn consent, AE, LOE will be imputed as non-responder. • Missing data due to any other reason including COVID-19 will be imputed using multiple imputation (MI)	Proportion of response/ CMH test adjusted by randomization strata

	Estimands			
Endpoint Category	**Endpoints**	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary/Analysis Method**
Key Secondary (Continuous)	• Percent change in EASI score from baseline to week 16 • Percent change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score	FAS	The intercurrent events will be handled as follows: • Discontinuation of study intervention: Data collected after the patient discontinued treatment will be included in the analyses (treatment policy strategy). • Initiation of rescue treatment: data after rescue treatment will be assigned by postbaseline worst-observation- carried-forward (WOCF) (hypothetical strategy). If there is no post-baseline assessment, the baseline value will be used (hypothetical strategy). Missing data imputation rules: • Missing data due to withdrawn consent, AE, or lack of efficacy will be imputed by postbaseline WOCF. If there is no post-baseline assessment,	Mean Change from baseline/ ANCOVA model with treatment and randomization strata as covariates

	Estimands			
Endpoint Category	**Endpoints**	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary/Analysis Method**
			the baseline value will be used. • Missing values due to other reasons including COVID-19 will be imputed by MI approach	

5.6.1. Analysis of Primary/Co-Primary Efficacy Variable

The Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline weight group: ≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3 and 4), and region/country (North America, Europe)) will be used for the analysis of percentage of patients with IGA 0 or 1 at week 16. Similar procedures will be used for percentage of patients with EASI-75 at week 16. At the time of this SAP, all patients for this study have been randomized. The smallest stratum (region = EU, baseline weight<15 kg, IGA=3) has 2 subjects only. All other strata have more than 10 patients. In all statistical analysis utilizing stratification factors in CMH test, stratum (region = EU, baseline weight<15 kg, IGA=3) will be combined with the stratum (region = EU, baseline weight >= 15 kg, IGA=3).

Handling of dropouts or adjudicated rescue treatment or missing value for the binary response variables as the primary analysis:

- If a patient withdraws consent from the study or discontinues due to AE or lack of efficacy (LOE), this patient will be counted as a non-responder for the time points after withdrawal.
- To account for the impact of rescue treatment on the efficacy effect: if rescue treatment is used (see Section 4.3, Appendix 1, and Appendix 6 for rescue treatment), the patient will be specified as a non-responder from the time the rescue treatment is used.
- If the patient has the missing value at week 16 due to any other reasons including COVID-19, the data will be imputed using multiple imputation (MI) based on all observed values as described below:
- The underlying continuous (e.g. EASI) or categorical variable (e.g. IGA) will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI using the following steps.
  - **Step 1:** The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345. 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 seed number 54321 and adjustment for covariates including treatment groups, randomization strata (baseline weight group, baseline IGA and region), and relevant baseline variables. For the categorical variable, such as IGA, a logistic regression under monotone option will be used.

Based on each imputed data, the response status (responder or non-responder) will be determined for each subject.

Once imputations are made, the week 16 data (binary response) of each of the 40 complete datasets will be analyzed using CMH test. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula. An appropriate transformation (such as Wilson-Hilferty transformation) of CMH test statistics can be used in Rubin's formula (Ratitch et. al 2013).

Sensitivity analyses:

Sensitivity analysis on primary and co-primary efficacy endpoints will be performed using the Tipping-point analysis method.

To assess the robustness of primary analysis results, a delta-adjusting pattern-mixture approach for tipping point analysis (2013, Ratitch) under MNAR (missing not at random) assumption, will be conducted for the co-primary endpoints. The impact from missing data on the comparisons in proportion of patients achieving IGA 0/1 (co-primary endpoint: EASI-75, **only in European Union [EU] and EU Reference Market Countries**) at week 16 between dupilumab and placebo control group will be examined as follows.

- A sequence of analyses will be performed with the adjustment to artificially decrease the response rate in dupilumab group and increase the response rate in placebo group with a fixed and definite set of values for data imputation.
- For each combination of increasing response rate in placebo and decreasing response rate in dupilumab, multiple imputed datasets will be generated and analyzed using CMH test. The results obtained from multiple imputed datasets will be combined to generate statistical inference, i.e. p-value and treatment difference between 2 treatment groups.
- A "tipping point" will be identified while the result is no longer statistically significant (i.e. p-value >0.05).

5.6.2. Analyses of Secondary Efficacy Variables

All secondary endpoints will be evaluated based on the FAS population.

The binary secondary efficacy endpoints will be analyzed using the same approaches used for the analysis of the primary endpoints as described in Section 5.6.1.

The continuous endpoints (e.g. EASI, worst scratch/itch NRS score) will be analyzed using analysis of covariance (ANCOVA) model with treatment, randomization strata (baseline weight group: ≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3 and 4), region/country (North America, Europe)) and relevant baseline value included in the model as the primary analysis method. The missing data for continuous endpoints will be imputed by the pattern-mixture

approach (MI-WOCF Method). The WOCF approach will be used for data after rescue or missing due to withdrawn consent, AE, and lack of efficacy. To be specific, the missing data will be imputed by postbaseline worst-observation-carried-forward (WOCF) if there is at least one non-missing postbaseline value or by baseline value if there is no postbaseline value. The multiple imputation (MI) approach will be used for the missing due to other reasons, including reasons due to COVID-19. The MI will be performed based on all observed data before the imputation by WOCF approach. To account for the uncertainty in the imputation, missing data from the FAS will be imputed 40 times to generate 40 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 MI procedure using seed number 12345. 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 seed number 54321 and adjustment for covariates including treatment groups, randomization strata (baseline weight group, baseline IGA and region), and relevant baseline.

Once imputations are made, the week 16 data of each of the 40 complete datasets will be analyzed using ANCOVA model with treatment, randomization strata (baseline weight group, baseline IGA and region), and relevant baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, the baseline value and the randomization strata (baseline weight group, baseline IGA and region)
- Measured endpoint values at every clinic visit (e.g. week 1, 2, 4, 8, 12 and week 16 for EASI)

Mean weekly dose of low potency TCS

The mean weekly dose of low potency TCS use during the treatment period endpoints will be analyzed using an ANCOVA model with treatment, randomization strata (baseline weight group, disease severity and region) and relevant baseline variables included in the model.

Similar analysis will be carried out for medium and/or high potency TCS.

Descriptive statistics will be provided for the mean of caregiver missed workdays (CMW) from baseline to week 16 for each treatment group.

Onset of action analysis,

Onset of action in percent change from baseline weekly average of daily worst scratch/itch NRS score can be assessed by providing a nominal p-value at each assessment visits. The analysis will be carried out on the FAS population only. Using this analysis, the first assessment visit at which $p < 0.05$ for the difference from placebo in the weekly average of daily worst scratch/itch NRS

score that remains $p < 0.05$ at subsequent weekly measurements through week 16 can be identified. The similar analysis will be carried out on the following binary responses:

- IGA 0/1
- EASI-75
- Improvement (reduction) of weekly average of daily worst itch NRS score $\geqslant 3$ from baseline
- Improvement (reduction) of weekly average of daily worst itch NRS score $\geqslant 3$ from baseline.

5.6.3. Adjustment for Multiple Comparison

Multiplicity Considerations

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints of dupilumab versus placebo. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in below table (all comparisons are with the placebo).

Level	Endpoints	Testing Order
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	1
Co-primary endpoint for EMA and EMA Reference Market Countries only, key secondary for US	Proportion of patients with EASI-75 (>=75% improvement from baseline) at week 16	2
Secondary endpoints	Percent change in EASI score from baseline to week 16	3
	Percent change from baseline to week 16 in weekly average of daily worst scratch/itch score	4
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline	5
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline	6
	Proportion of patients with EASI-50 at week 16	7
	Proportion of patients with EASI-90 at week 16	8
	Change from baseline in percent BSA affected by AD	9
	Change from baseline to week 16 in POEM	10
	Percent change from baseline to week 16 in SCORAD	11
	Change from baseline in Patient's sleep quality NRS	12
	Change from baseline in Patient's skin pain NRS	13
	Change from baseline in DFI	14
	Change from baseline to week 16 in CDLQI	15
	Change from baseline to week 16 in IDQOL	16

5.6.4. Subgroup Analysis

Subgroups for the primary endpoint (or co-primary endpoints for EU and EU reference countries) and key secondary endpoints will be analyzed based on the FAS.

Primary endpoints (or co-primary endpoints for EU and EU reference countries) and secondary endpoints those are in the hierarchical procedure (Section 5.6.3) will be analyzed in a similar fashion as in the main analysis for the severe AD subgroup (IGA = 4). Nominal p-values will be provided.

The analysis method for the subgroups will be the same as the primary analysis described in Section 5.6.1, and Section 5.6.2, as appropriate. If for any reason such as due to small number of patients in a subgroup, the model-based inferential statistics cannot be computed, or deemed inappropriate, only descriptive statistics will be provided.

Forest plots of the co-primary and key secondary efficacy endpoints across subgroups will be provided.

5.6.5. Analyses of Other Efficacy Variables

The analyses of other efficacy variables (binary and continuous endpoints) will be conducted in a similar fashion as the primary analysis described in Sections 5.6.1 and 5.6.2. unless otherwise noted in the individual descriptions of other efficacy variables or deemed inappropriate.

5.7. Analysis of Safety Data

The analysis of safety and tolerability will be performed based on the SAF.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs and 12-lead ECG.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables and vital signs are defined in Appendix 5. A treatment-emergent PCSV is any PCSV which developed or worsened in severity compared to baseline during the treatment and/or follow-up period. The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

In addition, the summary of safety results (including TEAEs, clinical laboratory, vital signs and ECG) will be performed for subjects who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic in each study part, respectively if deemed appropriate. The summary will be performed for pre-, during, and post-COVID-19 periods for patients impacted by COVID-19, if deemed appropriate.

5.7.1. Adverse Events

The number and proportion of patients reporting TEAEs will be summarized overall during the study, during the week 16 treatment period, and during the follow-up period separately, sorted by decreasing frequency of SOC and PT in the dupilumab group.

AE incidence tables will be presented by treatment group for the SAF as well as for selected subgroups. TEAE summaries will present the number (n) and percentage (%) of subjects experiencing a TEAE by SOC and PT, sorted by decreasing frequency of SOC and PT for the dupilumab treatment group. Multiple occurrences of AEs of the same PT (or SOC) in the same subject will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for subjects with multiple instances of the same event. The denominator for computation of percentage is the number of patients in each treatment group for the corresponding analysis period as specified in Section 3.2.

An overall summary of TEAEs will be provided with number and proportions of patients with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI)

- TEAE leading to death
- TEAE leading to permanent treatment discontinuation

Detailed summaries of TEAEs will include:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs (for HLTs: Injection site reactions, Herpes viral infections) by SOC/HLT/PT
  - TEAEs by PT
  - Common TEAEs by SOC/PT (incidence with PT ⩾5%)
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - TEAEs related to study medication as assessed by the investigator by SOC/PT
  - Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
- Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/PT
  - Serious TEAEs related to study medication as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- Fatal TEAE by SOC/PT
- AESI by AESI category (Appendix 4) and HLT/PT

The time to first AESIs (TEAE category) will be assessed by Kaplan-Meier estimates (K-M plot). In order to detect any safety signals, the hazard ratio (HR) will be provided together with the corresponding 95% confidence interval (CI) for the selected adverse events during the treatment period only. Hazard ratios will be calculated using a Cox model including treatment group and randomization strata as factors. The time is defined as the date of first specific event – the date of first dose + 1. Patients without a specific event will be censored at the end of the treatment period. Graphs of cumulative incidence rate over time may be provided by treatment group for selected TEAEs leading to permanent discontinuation of study treatment.

5.7.2. Analysis of Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit

- The number (n) and percentage (%) of subjects with treatment emergent PCSVs. This summary will be provided based on all patients in the SAF as well as in the subgroup of SAF patients who did not meet the PCSV criterion at baseline.
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

5.7.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSV
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

5.7.4. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

5.7.5. Analysis of Physical Exams

The number (n) and percentage (%) of patients with abnormal physical exams will be summarized at baseline, end of treatment period and end of study by treatment group. Shift table for physical exams status will be provided. A summary of treatment-emergent abnormal findings will be provided, as appropriate.

5.8. Analysis of Pharmacokinetic Data

The following analyses will be conducted:

- Descriptive statistics of functional dupilumab concentrations in serum at each sampling time by dose
- Graphical presentations of median and mean (+/- SD) functional dupilumab concentration in serum vs nominal time profiles
- Graphical presentations of individual functional dupilumab concentration in serum vs actual sampling time profiles
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum.

No formal statistical analysis will be performed.

5.9. Analysis of Immunogenicity Data

5.9.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.7 will be summarized using descriptive statistics in the ADA analysis set.

Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set.

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative subjects
  - Number (n) and percent (%) of pre-existing immunoreactivity subjects
- Number (n) and percent (%) of treatment-emergent ADA-positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA-positive patients

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.9.2. Analysis of Neutralizing Antibodies (NAb)

Samples positive in the ADA assay will be further characterized for the presence of neutralizing antibodies (NAb) for dupilumab. The absolute occurrence (n) and percent of patients (%) with NAb status (positive or negative) will be provided for patients in the NAb analysis set.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Association of immunogenicity with exposure

Potential association between immunogenicity variables and systemic exposure to dupilumab will be explored by treatment groups. Plots of dupilumab concentration may be provided for analyzing the potential impact of treatment-emergent, persistent ADA response and titer (high, moderate or low) and NAb on PK profiles.

5.10.2. Immunogenicity and Safety/ Efficacy

Potential association between immunogenicity variables and safety events will focus on the following events:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])

- Anaphylactic Reaction (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and the co-primary efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following ADA response categories:

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points
- Patients with persistent ADA response
- NAb positive patients, that is patients who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer level in treatment-emergent or treatment-boosted ADA positive patients:
  Low (titer <1,000), Moderate (1,000 ≤ titer ≤ 10,000), and High (titer >10,000)

5.11. 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:

- TARC
- total serum IgE
- Serum Immunoglobulin profile (IgG/IgM/IgA)
- Lactate dehydrogenase (LDH)

The Wilcoxon signed-rank test will be used to test if the change or percentage change from baseline value is significantly different from zero. P-value will be reported.

Exploratory analyses for the difference between dupilumab groups and placebo of the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group as a fixed effect, and the relevant baseline values as covariate. Missing values will be imputed by LOCF method for visits between post-baseline and week 16. After week 16, no imputation will be made. P-value for difference from placebo will be provided.

Relationship of baseline TARC and baseline IgE with the following clinical endpoints will be explored using ANCOVA model. The model includes the below clinical endpoint as the dependent variable and the log10 based transformed baseline biomarker data, treatment group and their interaction as the predictor variables. Model coefficients and P-value will be provided.

- Percent change from baseline to week 16 in EASI score
- Percent change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score

- Change from baseline to week 16 in percent BSA affected by AD
- Percent change from baseline to week 16 in SCORAD

Relationship of baseline TARC and baseline IgE with the following clinical endpoints will be explored using the logistic model. The model includes the responder/non-responder of the below clinical endpoints as the dependent variable and the log10 based transformed baseline biomarker data, treatment group and their interaction as the predictor variables. Model coefficients and P-value will be provided to indicate significance of the correlation/association.

- IGA 0-1 at week 16
- EASI-75 at week 16
- Improvement (reduction) of weekly average of worst scratch/itch scale ≥4 from baseline to week 16

Association of positivity to at least one antigen-specific IgE with the following clinical endpoints may be explored using CMH test stratified by randomization strata. The risk ratio and P-value will be provided.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of worst scratch/itch scale ≥4 from baseline to week 16

All above analyses will be performed on the FAS for

- All observed data, regardless if rescue treatment is used or data is collected after study drug withdrawal
- All observed data with censoring after rescue treatment use

The proportion of patients for whom biomarker concentrations “normalize” (shift from above normal to within the normal range) at Week 16 will also be evaluated.

The additional analysis will be performed on the following biomarkers at week 16:

- Serum total IgE
- Serum LDH

Serum total IgE and LDH have established clinical assays; the upper limit of normal (ULN) from the central lab reference range will determine the threshold for normal vs. elevated status.

Summary tables with normal/elevated status for serum total IgE and LDH at baseline and each post-baseline visit (until end-of-study) will be provided by treatment group.

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 of the study for all measurements will be the latest available valid measurement taken prior to the first administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of worst scratch/itch scale is defined in Section 4.4.2.

The following rules specify the determination of baseline by both date/time information:

1. For the AE, lab, PK and ADA data, 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, lab, PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen- failure subject ID or enrolled subject ID.

6.2. General Data Handling Conventions

For the laboratory safety variables data, if the data fall below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention Missing Data

Missing data will not be imputed in the 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. 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 event start date

AE start date will be used for AE classification and analysis of AESIs. 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 the 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 event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead.

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

If start month is missing, and 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 inform 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 in line with the protocol which specifies to collect up to 2 years of prior 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 end of study 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 end of study 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.

PCSV

Patients who had a post-baseline PCSV but a missing baseline value will be regarded as having a treatment emergent PCSV.

6.4. Analysis Visit Window

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG, ADA) will be summarized by the study scheduled visits described in the study protocol and SAP "Schedule of Events". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination (ET) visit have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The analysis visit windows are created per study Schedule of Events (SOE) table for each parameter and will be applied if the data from study scheduled visits are unavailable. The following general rules will be applied to unscheduled visit and/or early termination (ET) visit mapping for each parameter.

1. If ET visit falls in an analysis window which already has no missing observed value of this parameter from the scheduled visit, ET will be mapped to the next scheduled visit.
2. If both ET visit and unscheduled visit of the same parameter are available in the same analysis visit window, only ET visit will be mapped.
3. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visits will be mapped using the following rules:

a. The closest unscheduled visit from the target day will be selected.
b. If multiple unscheduled visits exist on the same day, the first unscheduled visit will be used.

4. If mapping distance is greater than 2 weeks, the unscheduled visit will not be mapped.

Unscheduled visits and early termination (ET) visit will be mapped per the following analysis visit windows based on the visit schedule of each parameter as per Appendix 3.

Table 1A. Analysis Visit Window for Efficacy Endpoints IGA, EASI, SCORAD, BSA, GISS

Visit from SOE	Target Day	Analysis Visit Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 1	8	[2,11]
Week 2	15	[12, 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	169	[156, 183]
Week 28	197	>=184

* Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date +1) when date of assessment ≥ 1st injection date; otherwise study day = (date of assessment – 1st injection date). If patient never received any dose of study drug, randomization date will be used in place of 1st injection date.

Table 2: Analysis Visit Window for Efficacy Endpoints CDLQI, IDQOL, DFI, POEM, CMW, CGID, CGIC

Visit from SOE	Target Day	Analysis Visit Window Based on Study day*
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	169	[156, 183]
Week 28	197	>=184

* Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date +1) when date of assessment ≥ 1st injection date; otherwise study day = (date of assessment – 1st injection date). If patient never received any dose of study drug, randomization date will be used in place of 1st injection date.
**Not applicable for CGIC.

Table 3: Analysis Visit Window for PASQ

Visit from SOE	Target Day	Analysis Visit Window Based on Study day*
Screening	<1	<1
Baseline	1	1**
Week 4	29	[2, 71]
Week 16	113	[72 155]
Week 28	197	>=156

* Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date +1) when date of assessment ≥ 1st injection date; otherwise study day = (date of assessment – 1st injection date). If patient never received any dose of study drug, randomization date will be used in place of 1st injection date.

Table 4: Analysis Visit Window for Safety labs, Vitals, PK and Biomarkers

Visit from SOE	Target Study Day in Part B a	Vital signs	Physical examination, ECG, Height, Weight	Lab*	PK, ADA	TARC[#], Serum Immunoglobulin profiling, antigen-specific IgE
Baseline	1	≤1	≤1	≤1	≤1	≤1
Week 1	8	[2, 11]				
Week 2	15	[12, 22]				
Week 4	29	[23, 43]		[2, 71]	[2, 43]	[2, 71] [#]
Week 8	57	[44, 71]			[44, 71]	
Week 12	85	[72, 99]			[72, 99]	
Week 16	113	[100, 127]	[2, 155]	[72, 155]	[100, 127]	[72, 155][#] [2, 155]
Week 20	141	[128, 155]			[128, 169]	
Week 24	169	[156, 183]				
Week 28	197	>= 184	>= 156	>=156	>= 170	>= 156

*Hematology and Blood Chemistry only.
[#]Only for TARC which was collected at baseline, Day 29, Day 113/EOT and Day 197/EOS.
Note that both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values for laboratory, vital signs or ECGs as well as the baseline values.

Rules for visit windows of ePRO data collected daily using eDiary:

For the daily collected ePRO data (e.g. Pruritus worst scratch/itch NRS, skin pain NRS, sleep quality NRS [patient and caregiver], CNSQ), 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 diary study day -7 to -1 = BL, 1 to 7 = week 1, 8 to 14 = week 2, etc, with 7 days interval between visit windows.

6.5. Statistical Technical Issues

None.

7. INTERIM ANALYSIS

No interim analysis is planned.

The primary analysis may be performed when the last patient completes 16 weeks of treatment duration in order to expedite the submission to regulatory agencies. No changes in the conduct of the study will be made based on this primary analysis. The assessment of co-primary and secondary endpoints performed during the analysis will be the final analysis of the co-primary endpoint and secondary endpoints. Hence, there will be no need for alpha adjustment due to the primary analysis.

In order to maintain study integrity (with respect to the post-treatment follow-up visits, safety visits, and analyses) in the event a decision is made to perform the primary analysis, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the primary analysis and all related activities, restrict other clinical team members and other sponsor personnel from access to individual patient treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions for the following post treatment analyses. However, the dedicated team can participate in the analysis following the final database lock.

8. SOFTWARE

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

9. REFERENCES

Al-Naqeeb J, Danner S, Fagnan LJ, et al. The Burden of Childhood Atopic Dermatitis in the Primary Care Setting: A Report from the Meta-LARC Consortium. J Am Board Fam Med. 2019;32(2):191-200.

Czarnowicki T, Esaki H, Gonzalez J, Malajian D, Shemer A, Noda S, Talasila S, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen $(CLA)^+$ T_H2/T_H1 cell imbalance, whereas adults acquire CLA^+ T_H22/T_C22 cell subsets. J Allergy Clin Immunol. 2015.

ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Hanifin JM, Thurston M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol. 2001; 10: 11-18.

Ileli S, von Mutius E, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. America Academy of Allergy, Asthma and Immunology. 2004; doi:10.1016/j.jaci.2004.01.778.

Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens, RG. The family impact of childhood atopic dermatitis: the dermatitis family impact questionnaire. Br J Dermatol. 1998;138:107-13.

Lewis-Jones MS, Finlay AY. The Childrens' Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995 Jun;132(6):942-9. PubMed PMID: 7662573.

Proudfoot LE, Powell AM, Ayis S, Barbarot S, Torres EB, Deleuran M, et al. The European treatment of severe atopic eczema in children taskforce (TREAT) survey. Br J Dermatol. 2013;169:901-09.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc., 1987.

Ratitch Bohdana, Lipkovich, IIya et. al. Combining Analysis Results from Multiply Imputed Categorical Data, PharmaSUG 2013 - Paper SP03

Schmitt J, Schakel K, et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator initiated double-blind placebo-controlled multicentre trial. Brit J Dermatol. 2009; journal compilation:1-8.

Severity scoring of Atopic Dermatitis: The SCORAD index. Consensus report of the European Task Force on Atopic Dermatitis. Dermatol. 1993;186:23-31.

Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003;112(6):S118-27.

Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. Arch Dis Child. 1997;76(2):159-62.

Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens, RG. The family impact of childhood atopic dermatitis: the dermatitis family impact questionnaire. Br J Dermatol. 1998;138:107-13.

APPENDIX 1. PROHIBITED AND RESCUE MEDICATIONS

Low potency steroids (permitted)	**Medium potency steroids (permitted as rescue, prohibited otherwise)**
Hydrocortisone acetate 1% cream / Hydrocortisone 1% cream (provided to sites by sponsor) Desonide 0.05% cream Alclometasone dipropionate 0.05% cream	Triamcinolone acetonide 0.1% ointment (provided to sites by sponsor) Triamcinolone acetonide 0.1% cream Fluticasone propionate 0.05% cream Fluocinolone acetonide 0.025% ointment
High Potency steroids (permitted as rescue, prohibited otherwise)	**Very high potency steroids (prohibited)**
Mometasone furoate 0.1% ointment Triamcinolone acetonide 0.5% ointment	Clobetasol propionate 0.05% ointment Betamethasone dipropionate 0.05% ointment

This is a representative list of TCS to be used in the study based on the American Academy of Dermatology classification. Starting on day -14, all patients will be required to initiate treatment with a low potency TCS using a standardized regimen. Based on investigator discretion, low/mild potency TCS may also be used on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.). Hydrocortisone acetate 1% cream / hydrocortisone 1% cream should be used unless there are known side effects to these agents or due to non-availability due to any reason. In those cases, other low potency TCS such as desonide 0.05% cream or alclometasone dipropionate 0.05% cream can be used. The use of medium/high potency steroids should be reserved for rescue. It is recommended that triamcinolone acetonide 0.1% ointment be used for rescue. However, other medium or high potency TCS may be used as per investigator discretion. The use of very high potency steroids is not allowed during the study.

APPENDIX 2. LIST OF ANALYSIS

Efficacy Analysis:

Parameter(s)	Analysis Populations	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
Investigator's Global Assessment (IGA) (Primary)	FAS	• IGA 0 to 1 (Categorical)	• CMH test adjusted by randomization strata (IGA Severity, Region, and Baseline weight)	Tipping point analysis	Yes
Eczema Area and Severity Index (EASI) (EASI-75 Co-primary, for EU only)	FAS	Categorical: • EASI 75 • EASI 50 • EASI 90 Continuous: • % change from baseline	•Categorical: CMH test adjusted by randomization strata for categorical variables • Continuous: Multiple imputation (MI) using pattern mixture ((MI-WOCF)) with ANCOVA for continuous variables	Tipping point analysis for co-primary endpoint only.	Yes; For EASI-75 and % Change from baseline
Pruritus worst scratch/itch score (NRS)	FAS	Categorical: • NRS score ≥3 • NRS score ≥4 Continuous: • % change from baseline • Change from baseline	•Categorical: CMH test adjusted by randomization strata for categorical variables • Continuous: Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	Yes for % change

Parameter(s)	Analysis Populations	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
Skin Pain NRS	FAS	• Change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
Sleep quality NRS	FAS	• Change from baseline [Patient, Caregiver]	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
Body Surface Area (BSA) Involvement of Atopic Dermatitis	FAS	• Change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA	No	No
SCORing Atopic Dermatitis (SCORAD)	FAS	Continuous: • % change from baseline Categorical: • SCORAD50 • SCORAD75 • SCORAD90	• Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables • CMH test adjusted by randomization strata for categorical variables	No	No
Dermatitis Family Index (DFI)	FAS	• Change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA	No	No
Global Individual Signs Score (GISS)	FAS	• Change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
Patient Oriented Eczema Measure (POEM)	FAS	• Change from baseline	• Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No

Parameter(s)	Analysis Populations	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
Children Dermatology Life Quality Index (CDLQI) (>= 4 years of age)	FAS	• Change from baseline	• Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
Infants' Dermatology Quality of Life Index (IDQOL) (< 4 years of age)	FAS	• Change from baseline	• Multiple imputation (MI using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
TCS	FAS	• Proportion of TCS medication-free days from baseline to week 16 • Mean weekly dose of TCS in grams for low potency TCS from baseline to week 16	• CMH test adjusted randomization strata • ANCOVA for continuous variables	No	No
Caregiver missed workdays (CMW)	FAS	• Mean of caregiver missed workdays	• Descriptive statistics by visit/time	No	No
Caregiver global impression of disease (CGID)	FAS	• Proportion of patients with No symptoms at week 16 • proportion of patients with No symptoms or Mild at week 16	CMH test adjusted randomization strata	No	No
Caregiver global impression of change (CGIC)	FAS	• Proportion of patients with ratings = "Much better" at week 16 • Proportion of patients with ratings = "Much better" or "Moderately better" at week 16	CMH test adjusted randomization strata	No	No

Parameter(s)	Analysis Populations	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
PASQ (for patients with Asthma)	FAS	• PASQ total score based on questions 3-6	Multiple imputation (MI using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
CNSQ (for patients with medical history of allergic rhinitis)	FAS	• Change from baseline in CNSQ score at week16	Multiple imputation (MI using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
IGA	FAS	• Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16	CMH test adjusted randomization strata	No	No
IGA and EASI	FAS	• Proportion of patients with IGA score 0 or 1 or EASI-90 at week 16	CMH test adjusted randomization strata	No	No

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	Yes for selected AE summary	No
Skin infection TEAE	SAF	Incidence of skin infection TEAE (excluding herpetic infections) through week 16	Descriptive summary (incidence)	No	No
TE-SAE	SAF	Incidence of treatment-emergent serious adverse events (SAE) through week 16	Descriptive summary (incidence)	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

APPENDIX 3. SCHDULE OF EVENTS FOR THE SCREENING, TREATMENT, AND FOLLOW-UP PERIOD (PART B)

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Screening/Baseline:																								
Inclusion/ Exclusion[22]	X		X																					
Parental Informed Consent[23]	X																							

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Unscheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Parental Informed Consent for Optional Genomic Sub-study[2]	X																							
Parental Informed Consent for Optional Vaccine Sub-study[3]	X																							

Study Procedure	Screening Period[24]		BL	Treatment Period																Follow-Up			Un-scheduled Visit[21]	ET Visit
	SCN	TCS Std				PV[1]		PV[1]	PV[1]	PV[1]		PV[1]	PV[1]	PV[1]		PV[1]	PV[1]	PV[1]	EOT			EOS		
Visit	**1**	**2**	**3**	**4**	**5**	**6**[1]	**7**	**8**[1]	**9**	**10**[1]	**11**	**12**[1]	**13**[1]	**14**[1]	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Parental Informed Consent for Optional Tape Stripping Sub-study (selected study sites only)	X																							

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Parental Informed Consent for Optional Use of Photographs (selected study sites only)[30]	X																							
Collect vaccination plan[4]	X																							

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Medical History	X																							
Ophthalmology Exam (patients with history of certain eye disorders)[32]	X																							
Demographics	X																							

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Randomization			X																					
Parent/ Caregiver e-diary training[5]	X	X																						
Treatment:																								
TCS application[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
TCS dispensation		X	X	X	X		X				X				X				X	X	X		X	
TCS accountability[7]			X	X	X		X				X				X				X	X	X	X	X	X
Administer Study Drug[8]			X[9]				X[9]				X[9]				X									

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Parent/ Caregiver Counseling for e-diary Completion		X	X	X	X		X				X				X				X	X	X		X	
Parent / Caregiver Recording of TCS Use via e-diary (daily)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Parent / Caregiver Recording of Emollient Use via e-diary (daily)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy[10]:																								

Study Procedure	Screening Period[24]		BL	Treatment Period																Follow-Up			Un-scheduled Visit[21]	ET Visit
	SCN	TCS Std				PV[1]		PV[1]	PV[1]	PV[1]		PV[1]	PV[1]	PV[1]		PV[1]	PV[1]	PV[1]	EOT			EOS		
Visit	**1**	**2**	**3**	**4**	**5**	**6**[1]	**7**	**8**[1]	**9**	**10**[1]	**11**	**12**[1]	**13**[1]	**14**[1]	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Assessment of Pruritus (worst scratch/itch) NRS[11,12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Skin Pain NRS and Sleep Diary[12,26]			X	X	X		X												X			X		

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
IGA, EASI, SCORAD, BSA, GISS	X		X	X	X		X				X				X				X	X	X	X	X	X
CDLQI[12, 13] IDQOL[12, 13, 14,] DFI[12, 13] POEM[12, 14] Caregiver Missed Workdays	X		X		X		X				X				X				X	X	X	X	X	X

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
CGID	X		X		X		X				X				X				X	X	X	X	X	X
CGIC					X		X				X				X				X	X	X	X	X	X
PASQ[12,14,28]	X		X				X												X			X	X	X
CNSQ[12,14,29]			X				X												X			X		

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Photograph AD Areas (Selected Study Sites only)			X																X			X		X

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Safety:																								
Weight	X		X																X			X		X
Height	X																		X			X		X
Vital Signs	X		X[15]	X	X		X[15]				X[15]				X				X	X	X	X	X	X
Physical Examination	X		X																X			X	X	X
ECG[27]	X																		X			X	X	X

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Adverse Events[33]	X	X	X[15]	X	X	X	X[15]	X	X	X	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[16]:																								
Hematology	X						X												X			X	X	X
Blood Chemistry	X						X												X			X	X	X

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
HIV, HBsAg, HBsAb, HBcAb, Hepatitis C Ab, TB[17]	X																							
Serum sample for vaccination response[18]		X	X	X	X		X				X				X				X	X	X	X	X	X
Biomarkers[19]:																								

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
TARC			X				X												X			X		X
Serum Immunoglobulin profiling, antigen-specific IgE			X																X			X		X

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Research Testing[25]:																								
Optional DNA buccal sample[2]			X																					
Optional tape stripping sample[31]			X																X					
PK/Drug Concentration and ADA Samples[25]:																								

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
PK/Drug concentration sample[19]			X				X				X				X				X	X		X	X	X
ADA sample[20]			X																X			X	X	X

Note: AD = atopic dermatitis; ADA = anti0drug antibody; AESI=adverse event of special interest; BL = Baseline; BSA = body surface area; CDLQI = Childrens' Dermatology Life Quality Index; CGIC = Caregiver Global Impression of Change; CGID = Caregiver Global Impression of Disease; CNSQ = Caregiver-Reported Nasal Symptom Questionnaire; DFI = Dermatitis Family Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; e-diary = electronic diary; EOT = End of treatment; EOS = End of Study; ET = Early Termination; GISS = Global Individual Signs Score; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; IDQOL = Infants' Dermatology Quality of Life Index; IGA = Investigator Global Assessment; IgE = immunoglobulin E; NRS = numeric rating scale; PASQ = Pediatric Asthma Symptom Questionnaire; PK = pharmacokinetic; POEM = Patient Oriented Eczema Measure; PV = phone visit; Q4W = every 4 weeks; SCN = screening; SCORAD = SCORing Atopic Dermatitis; TARC = thymus and activation regulated chemokine; TB = tuberculosis; TCS = topical corticosteroid; Std = standardization.

[1] The site will contact the parent/caregiver by telephone to conduct these visits.
[2] For patients whose parents or legal guardians agree to their participation and provide a specific written informed consent for the optional genomics sub-study (DNA sample collection), DNA sample should be collected at the day 1 visit but can be collected at any visit during the study.
[3] Parents/caregivers of patients will be encouraged to provide vaccination plans for any vaccines which are in line with the patient's age, and local medical practice (live attenuated vaccines are excluded) during the study. Parents or legal guardians of patients planning to receive any vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples (a pre-vaccine and post-vaccine sample) for assay of vaccine IgG in serum for each vaccination.
[4] The study team on site will collect information from the parents/caregivers regarding the vaccinations planned during the next 6 months from screening. The study team should refer to the patient's medical records and national vaccination schedule to gather this information. The study team can also contact the patient's primary physician and/or pediatrician to gather this information.
[5] Training of parents/caregivers regarding completion of e-diary at visit 1 to record a) completion of assessment of pruritus NRS (worst scratch/itch scale), skin pain NRS, sleep diary, and CNSQ and b) TCS and emollient usage. Provide additional training as necessary based on review of e-diary use.
[6] As per the standardized regimen outlined in Section 5.2 of the study protocol.
[7] The type, amount, and potency of topical products used during the study will be recorded. The amount of TCS used will be determined by weighing the tube at each visit through the end of the study.
[8] The dose regimens, including frequency of administration in part B are placebo Q4W or dupilumab Q4W tiered fixed-dose (200 mg for patients ≥5-<15kg or 300 mg for patients ≥15-<30 kg).
[9] Patients will be monitored at the study site at visits 3, 7 and 11 for a minimum of 2 hours after study drug administration.
[10] Assessments/procedures should be conducted in the following order: patient reported outcomes, investigator assessments, safety and laboratory assessments, administration of study drug.
[11] The assessment will be recorded daily. Parents/caregivers will complete an e-diary daily to record pruritus (worst scratch/itch) NRS in patients.
[12] The questionnaires will be administered only to those patients and/or parents/caregivers who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries). It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study.
[13] Childrens' Dermatology Life Quality Index (CDLQI) for patients ≥4 years of age, Infants' Dermatitis Quality of Life Index (IDQOL) for patients <4 years of age, Dermatology Family Index (DFI) to be completed by an adult family member of a child affected by dermatitis.
[14] Questionnaire will be completed by the parent/caregiver on behalf of the patient. It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study.
[15] Patients will be monitored at the study site at visits 3, 7, and 11 for a minimum of 2 hours after study drug administration. Vital signs (sitting systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) and AE assessments will be done at 30 minutes (±10 minutes) post-injection, and then at 2 hours (±15 minutes) post-injection.
[16] Samples will be collected before the injection of study drug.
[17] TB testing will be performed on a country-by-country basis, according to local guidelines, if required by regulatory authorities or ethics boards.
[18] Optional collection of blood for assay of vaccine IgG in serum for each vaccine administered. The first sample should be drawn within 6 weeks prior to vaccination, and the second sample should be drawn 3 to 4 weeks (maximum 6 weeks) after vaccination. Vaccinations should be performed in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, samples can also be drawn at unscheduled visits.
[19] Samples to measure functional dupilumab concentration and biomarkers will be collected prior to injection of study drug.
[20] Samples to be collected prior to injection of study drug. Patients who are ADA positive at their last study visit (early termination, or end of study) and who do not participate in the OLE may be considered for follow-up based on the overall clinical presentation at that time. Patients who are considered for follow-up may be asked to return to the clinic to have additional samples collected for analysis.
[21] The specific assessments that will be performed at the unscheduled visit will depend upon the reason for the unscheduled visit. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional PK and ADA samples may be collected at or near to the event as practically possible.
[22] Eligibility based on age at time of screening visit.

[23] Assent collected from patient, if applicable, as per local regulatory (competent authority/ethics) guidelines, based upon the age and level of maturity of the patient.
[24] The length of the screening period is not fixed but must not exceed 56 days (including TCS standardization). The length of the TCS standardization period is fixed at 14 days.
[25] Any unused serum samples collected for dupilumab concentrations or ADA measurements may be used for exploratory biomarker research related to AD, inhibition of the IL-4Rα pathway with an antibody, treatment response (PD and or predictive), or vaccine response, as well as to investigate unexpected AEs or to identify markers associated with adverse reactions.
[26] Pain and sleep will be assessed daily for the 14 days leading up to the baseline visit, the 7 days leading up to the week 1 visit, the 7 days leading up to the week 2 visit, the 7 days leading up to the week 4 visit, the 7 days leading up to the week 16 visit, and 7 days leading up to the week 28 visit. Parents/caregivers will complete a daily e-diary on these days to record skin pain and sleep in patients.
[27] ECGs should be conducted prior to collection of blood samples at visits requiring blood draws.
[28] Completed only for the subset of patients with ongoing asthma.
[29] Completed only for the subset of patients with a medical history of allergic rhinitis. Caregivers will be instructed on using the e-diary to record the CNSQ for 14 days before baseline/day 1 and for the 7 days preceding visits 7, 19, and 22 (weeks 4, 16, and 28).
[30] Optional parental informed consent for use of photographs for educational/marketing purposes (selected study sites only).
[31] An optional tape stripping sub-study may be performed at a subset of study sites. Parents or legal guardians who agree for their child to participate in the tape stripping sub-study will be required to sign a separate sub-study ICF before collection of the samples. Baseline samples should be collected on day 1/baseline (pre-dose). A second sample will be collected at week 16.
[32] Patients who have history of certain eye disorders (conjunctivitis, blepharitis or keratitis) within 12 months prior to the screening visit will be referred to an ophthalmologist (see protocol Section 6.2.3.6). Any baseline findings will be documented as part of the patient's medical history and/or physical exam, as appropriate.
[33] Any patient who experiences an AESI related to an eye disorder will be referred to an ophthalmologist (see protocol Section 7.2.3).

APPENDIX 4. AESI AND OTHER AES CRITERIA

AESI	Search Criteria
Anaphylactic reactions	Narrow SMQ for "anaphylactic reaction"
Systemic hypersensitivity reactions	Narrow SMQ for "hypersensitivity" Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Helminthic infections	Include the following HLTs 1. HLT = Cestode infections 2. HLT = Helminthic infections NEC 3. HLT = Nematode infections 4. HLT = Trematode infections
Any severe type of conjunctivitis or blepharitis	Broad CMQ Conjunctivitis PTs Conjunctivitis Conjunctivitis allergic Conjunctivitis bacterial Conjunctivitis viral Atopic keratoconjunctivitis Blepharitis Dry eye

	Eye irritation Eye pruritus Lacrimation increased Eye discharge Foreign body sensation in eyes Photophobia Ocular hyperaemia Conjunctival hyperaemia Xerophthalmia, and PTs: Bacterial blepharitis Blepharitis allergic AND Serious AE= "Yes" OR Severity= "severe"
Keratitis	Narrow SMQ for "corneal disorders"
Clinically symptomatic eosinophilia	HLT = Eosinophilic disorders OR PT = Eosinophil count increased

	Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Other AEs	**Search Criteria**
Skin Infections	SOC = (**'Infections and infestations'**, **'Skin and subcutaneous tissue disorders'**)
Herpes Infections	HLT = **Herpes viral infections**
Injection Site Reactions	HLT = **Injection Site Reactions**

The search criteria are meant to assist the process of identification of TEAE of Special Interest/TEAE Syndrome. However, since these criteria might not be exhaustive in some cases or may not be specific in other cases. Hence an additional blinded review of all PTs in the database may be performed by the Medical monitor, based on medical judgement, to identify any TEAE of Special Interest/TEAE Syndrome that might have been missed by the criteria or to identify any TEAE may been inaccurately assigned as AESI by the algorithmic search

APPENDIX 5. PCSV CRITERIA

Criteria for Treatment-Emergent Potentially Clinical Significant Value for Pediatric Patients (>= 6months to <6 years old)

Age range	Parameter	TE PCSV	Comments
	Vital Signs		Ref. : Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
6 months - <1 year	**HR**	≤72 bpm and decrease from baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm	

1- <3 years	**HR**	≤63 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
3-<6 years	**HR**	≤59 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
6 months -<1 year	SBP	≤70 mmHg and decrease from baseline ≥20 mmHg ≥110 mmHg and increase from baseline ≥20 mmHg	
1 - <3 years	SBP	≤70 mmHg and decrease from baseline ≥20 mmHg ≥116mHg and increase from baseline ≥20 mmHg	
3-<6 years	SBP	≤70 mmHg and decrease from baseline ≥20 mmHg ≥121 mHg and increase from baseline ≥20 mmHg	

6 months -< 1 year months	DBP	≤34 mmHg and decrease from baseline ≥10 mmHg ≥72mHg and increase from baseline ≥10 mmHg	
1-<3 years	DBP	≤34 mmHg and decrease from baseline ≥10 mmHg ≥77mHg and increase from baseline ≥10 mmHg	
3 - <6 years	DBP	≤34 mmHg and decrease from baseline ≥10 mmHg ≥83mHg and increase from baseline ≥10 mmHg	
6 months - <6 years	Temperature	Rectal, ear or temporal artery: ≥102.2 °F/39.0 °C Oral or pacifier: >102.2°F/39.0°C Axillary or skin infrared: >102.2 °F/39.0 °C	
6 months - <1 year months	Respiratory rate	< 24 per minute and ≥ 24 per minute at baseline > 40 per minute and ≤ 40 per minute at baseline	
1 - <6 years	Respiratory rate	< 20 per minute and ≥ 20 per minute at baseline > 34 per minute and ≤ 34 per minute at baseline	

6 months - <6 years	Weight	≥5 % weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007
	Clinical Chemistry		Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005 ; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
6 months - <6 years	ALT	≥3 ULN and baseline <3 ULN	Based on normal ranges: 5 to 45 U/L (Females 6 months-<6 years) 5 to 49 U/L (Males 6 months- <6 years)
6 months - <6 years	AST	≥3 ULN and baseline <3 ULN	Based on normal ranges: 9 to 50 U/L (Females 6 months-<6 years) 9 to 60 U/L (Males 6 months-<6 years)
6 months - <6 years	Alkaline Phosphatase (ALP)	≥1.5 ULN and baseline < 1.5 ULN	Based on normal ranges: 70 to 350 U/L (6 months-<1 year) 125 to 320 U/L (≥1- ≤3 years) 150 to 370 U/L (≥4- <6 years)

6 months - <6 years	Total Bilirubin	≥1.3 ULN and baseline < 1.3 ULN	CF = mg x 1.7 = µmol Based on normal ranges: ≤1 mg/dL
6 months - <6 years	Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin (TBILI) and TBILI ≥1.3 ULN) and (Direct Bilirubin ≤35% TBILI or TBILI <1.3 ULN) at baseline	CF = mg x 1.7 = µmol Based on normal range: 0 to 0.4 mg/dL
6 months- <6 years	ALT/AST and Total Bilirubin	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN)) at baseline	
6 months - <6 years	CPK	≥3 ULN and < 3 ULN at baseline	
6 months - < 1 year	Creatinine	>53 µmol/L or 0.6 mg/dL and ≤ 53 µmol/L or 0.6 mg/dL at baseline (Females 6 months- <1 year) >62 µmol/L or 0.7 mg/dL and ≤ 62 µmol/L or 0.7 mg/dL at baseline (Males 6 months- <1 year)	CF = mg x 8.8 = µmol
1- ≤3 years	Creatinine	>62 µmol/L or 0.7 mg/dL and ≤ 62 µmol/L or 0.7 mg/dL at baseline	

4- <6 years	Creatinine	>71 µmol/L or 0.8 mg/dL and ≤ 71 µmol/L or 0.8 mg/dL at baseline	
6 months - <6 years	Uric Acid	≥8.0 mg/dL or 476 µmol/L and <8.0 mg/dL or 476 µmol/L at baseline	CF = mg x 5.95 = µmol
6 months - <6 years	Blood Urea Nitrogen (BUN)	≥6.4 mmol/L or 18 mg/dl and <6.4 mmol/L or 18 mg/dl at baseline	
6 months - <6 years	Chloride	≤80 mmol/L or 80 mEq/L and >80 mmol/L or 80 mEq/L at baseline ≥115 mmol/L or 115 mEq/L and <115 mmol/L or 115 mEq/L at baseline	CF = 1
6 months - <6 years	Sodium	≤129 mmol/L or 129 mEq/L and >129 mmol/L or 129 mEq/L at baseline ≥150 mmol/L or 150 mEq/L and <150 mmol/L or 150 mEq/L at baseline	CF = 1
6months - ≤1 year	Potassium	≤3.5 mmol/L or 3.5 mEq/L and >3.5 mmol/L or 3.5 mEq/L at baseline ≥6.1 mmol/L or 6.1 mEq/L and <6.0 mmol/L or 6.0 mEq/L at baseline	
>1 - <6 years	Potassium	≤3.5 mmol/L or 3.5 mEq/L and >3.5 mmol/L or 3.5 mEq/L at baseline ≥5.5 mmol/L or 5.5 mEq/L and <5.5 mmol/L or 5.5 mEq/L at baseline	

6 months - <6 years	Calcium total	≤2.0 mmol/L or 8.0 mg/dL and >2.0 mmol/L or 8.0 mg/dL at baseline ≥2.9 mmol/L or 11.6 mg/dL and <2.9 mmol/L or 11.6 mg/dL at baseline	CF = mg x 0.025 = mmol
6 months - <6 years	Total Cholesterol	>6.20 mmol/L or 240 mg/dL and ≤6.20 mmol/L or 240 mg/dL at baseline	CF = g x 2.58 = mmol
6 months - <6 years	Triglycerides	>4.0 mmol/L or 350 mg/dL and ≤4.0 mmol/L or 350 mg/dL at baseline	After >12 hours of fast) CF = g x 1.14 = mmol
6 months - <6 years	Glucose	Hypoglycaemia: <2.7 mmol/L and ≥2.7 mmol/L at baseline (or < 50 mg/dL and ≥ 50 mg/dL at baseline) Hyperglycaemia: ≥10 mmol/L (unfasted) and < 10 mmol/L (unfasted) at baseline (or ≥180 mg/dl and <180 mg/dl at baseline); ≥7 mmol/L (fasted) and <7 mmol/L (fasted) at baseline (or ≥120 mg/dL and <120 mg/dL at baseline)	CF = g x 5.55 = mmol

	Hematology		Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006 ; Division of Microbiology and Infections Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995
6 - 23 months	WBC	<4.0 GIGA/L or 4,000 /mm3 and ≥ 4.0 GIGA/L or 4,000 /mm3 at baseline >20.0 GIGA/L or 20,000 /mm3 and ≤20.0 GIGA/L or 20,000 /mm3 at baseline	
2 - <6 years	WBC	<3.0 GIGA/L or 3,000 /mm3 and ≥ 3.0 GIGA/L or 3,000 /mm3 at baseline >16.0 GIGA/L or 16,000 /mm3 and ≤ 16.0 GIGA/L or 16,000 /mm3 at baseline	
6 months- <1 year	Lymphocytes (ALC)	<2.0 GIGA/L or 2,000 /mm3 and ≥ 2.0 GIGA/L or 2,000 /mm3 at baseline >17.0 GIGA/L or 17,000/mm3 and ≤17.0 GIGA/L or 17,000 /mm3 at baseline	

≥1 - <6 years	Lymphocytes (ALC)	<1.0 GIGA/L or 1,000 /mm3 and ≥ 1.0 GIGA/L or 1,000 /mm3 at baseline >10.5 GIGA/L or 10,500/mm3 and ≤10.5 GIGA/L or 10,500 /mm3 at baseline	
6 months - <6 years	Absolute Neutrophil Count (ANC)	<1.2 GIGA/L or 1,200 /mm3 and ≥ 1.2 GIGA/L or 1,200 /mm3 at baseline (3-24 months)	
6 months - <6 years	Eosinophils	(>0.5 Giga/L and >ULN) and (≤0.5 Giga/L or ≤ ULN at baseline)	
6 - 23 months	Hemoglobin	< 1.40 mmol/L or 9.0 g/dL and ≥ 1.40 mmol/L or 9.0 g/dL at baseline or any decrease ≥ 0.31 mmol/L or 2 g/dL	
2 - <6 years	Hemoglobin	< 1.55 mmol/L or10.0 g/dL and ≥ 1.55 mmol/L or10.0 g/dL at baseline or any decrease ≥ 0.31 mmol/L or 2 g/dL	
6 - 23 months	Hematocrit	< 0.29 l/l or 29 % and ≥ 0.29 l/l or 29 % at baseline > 0.42 l/l or 42 % and ≤0.42 l/l or 42 % at baseline	
2 - <6 years	Hematocrit	< 0.32 l/l or 32 % and ≥ 0.32 l/l or 32 % at baseline > 0.47 l/l or 47 % and ≤ 0.47 l/l or 47 % at baseline	

6 months - <6 years	Platelets	<100 GIGA/L or 100,000 /mm3 and ≥ 100 GIGA/L or 100,000 /mm3 at baseline > 700 GIGA/L or 700,000 /mm3 and ≤700 GIGA/L or 700,000 /mm3 at baseline	
	ECG parameters		Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
6 - 23 months	PR	≥140 ms and <140 ms at baseline	
2 - <6 years	PR	≥160 ms and <160 ms at baseline	
6 - 23 months	QRS	≥85 ms and <85 ms at baseline	
2 - <6 years	QRS	≥95 ms and <95 ms at baseline	
6 months - <6 years	QTc	Absolute values (ms) Borderline: 431-450 ms and <431 ms at baseline Prolonged*: >450 to <500 ms and ≤450 ms at baseline Additional: ≥500 ms and <500 ms at baseline Increase from baseline	**To be applied to QTcF** *QTc prolonged and DQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.

		Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	

APPENDIX 6. RESCUE TREATMENTS

Algorithm for RESCUE TREATMENTS

1. Not required to adjudicate rescue treatment:

a. Always considered rescue:

Following post-baseline medications (WHODD-coded) given for indications consistent with AD

- ATC2 = CORTICOSTEROIDS FOR SYSTEMIC USE unless used before day 15
- ATC2 = IMMUNOSUPPRESSANTS unless used before day 15
- Preferred Drug Name = Ciclosporin
- Preferred Drug Name = Methotrexate
- Preferred Drug Name = Mycophenolate sodium
- Preferred Drug Name = Mycophenolic acid
- Preferred Drug Name = Mycophenolate mofetil
- Preferred Drug Name = Azathioprine

b. Never considered rescue

- ATC2 = EMOLLIENTS AND PROTECTIVES
- ATC2 = VASOPROTECTIVES
- ATC2 = ANALGESICS
- ATC2 = ANTI-ACNE PREPARATIONS
- ATC2 = TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
- ATC2 = ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
- ATC2 = ANTIVIRALS FOR SYSTEMIC USE

- ATC2 = ANTIFUNGALS FOR DERMATOLOGICAL USE
- ATC2 = ANTISEPTICS AND DISINFECTANTS
- ATC2 = ANTIHISTAMINES FOR SYSTEMIC USE
- ATC2 = ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.
- ATC2 = GENERAL NUTRIENTS
- ATC2 = VITAMINS
- ATC2 = DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
- ATC2 = OPHTHALMOLOGICALS
- ATC2 = ANTIINFLAMMATORY AND ANTIRHERUMATIC PRODUCTS
- ATC2 = PSYCHOLEPTICS
- ATC4 = CORTICOSTEROIDS, WEAK (GROUP I)
- ATC1 = ANTIINFECTIVES FOR SYSTEMIC USE
- ATC1 = BLOOD AND BLOOD FORMING ORGANS
- ATC1 = ALIMENTARY TRACT AND METABOLISM
- ATC1 = MUSCULO-SKELETAL SYSTEM
- ATC2 = COUGH AND COLD PREPARATIONS
- ATC2 = CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, if used before Day 15
- Preferred Drug Name = Tacrolimus, if used before Day 15
- Preferred Drug Name = Pimecrolimus, if used before Day 15
- Preferred Drug Name= Crisaborole, if used before Day 15

A blinded review of all post-baseline medications to adjudicate rescue treatment, based on medical judgement, may be performed in addition. A listing of treatments classified as rescue/non-rescue in a manner inconsistent with the classification under #1 will be provided, along with supporting rationale.

2. Required to adjudicate rescue treatment:

- All other medications (not noted in **1** above) given for indications consistent with AD[2]
- Medications noted in **1a** above, when given for indications not consistent with AD

[2] Below is a list of indications consistent with AD based on PT level from concomitant medication/procedure data using MedDRA dictionary

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
Infections and infestations	Bacterial infections NEC	Eczema impetiginous	10051890
Infections and infestations	Skin structures and soft tissue infections	Dermatitis infected	10012470
Infections and infestations	Skin structures and soft tissue infections	Eczema infected	10014199
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis	10012431
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis atopic	10012438
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Eczema	10014184
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Neurodermatitis	10029263

Signature Page for VV-RIM-00152867 v1.0

ESig Approval	[redacted]000
ESig Approval	[redacted]000
ESig Approval	[redacted]-2021 13:21:38 GMT+0000

Signature Page for VV-RIM-00152867 v1.0 Approved