Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥12 to <18 years of age, with moderate-to-severe Atopic Dermatitis

Protocol: R668-AD-1526.03

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

Statistician: [redacted]

Clinical Trial Manager: [redacted]

Study Medical Director: [redacted]

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

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Head of BDM or designee (Approver)

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ	Asthma Control Questionnaire
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
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
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
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
MMRM	Mixed-effect model with repeated measures
NAb	Neutralizing Antibody

NRS	Numerical rating scale
PCS	Pruritus Categorical Scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
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 realize the analysis of data for the R668-AD-1526 study.

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

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 the most common inflammatory skin disease in childhood. The disease usually presents during early infancy and childhood, but it can persist into or start in adulthood. The disease affects 15% to 30% of children and 2% to 10% of adults in industrialized countries. Phase 1 of the International Study of Asthma and Allergies in Childhood showed a 1-year period prevalence rate as high as 20% in Australia, England, and Scandinavia. Often, AD constitutes the first step of the "atopic march" (progression from one atopic disease to another). Up to 60% of AD patients have concomitant asthma, allergic rhinitis, or food allergy.

There is currently a high unmet medical need for a safe and effective therapy for AD in children. 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 an important therapeutic role to help control mild disease and a supportive role 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). Topical corticosteroids reduce inflammation and pruritus, and are useful in controlling acute flares. 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 many times as an alternative to or in combination with TCS. However, 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 (refer to products' US prescribing information).

Systemic agents are used off label (cyclosporine, methotrexate, azathioprine, systemic steroids and mycophenolate mofetil) in the treatment of AD in children and lack robust evidence for the basis of use. All of these systemic agents have significant side effects, including stunted growth, diabetes, hypertension, 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.

As a biologic product that selectively targets the Th2 inflammatory pathway, dupilumab is being developed to provide a safe and efficacious alternative treatment for AD patients, including children. Dupilumab is a human monoclonal antibody that targets the IL-4 receptor alpha subunit (IL-4Rα), a component of IL-4 receptors Type I and Type II, as well as the IL-13 Type II receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Because up-regulation of IL-4 and IL-13 has been implicated as an important driver of AD, treatment with dupilumab may demonstrate efficacy in the treatment of this disease.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab as a monotherapy in patients ≥12 years to <18 years of age with moderate-to-severe AD.

1.2.2. Secondary Objectives

The secondary objective of the study is to assess the safety of dupilumab as a monotherapy in patients ≥12 years to <18 years of age with moderate-to-severe AD.

1.2.3. Modifications from the Statistical Section in the Final Protocol

- Removed the "or lasting ≥ 4 weeks" condition from the AESI criteria for any type of conjunctivitis or blepharitis (i.e. Any type of conjunctivitis or blepharitis (only events that are severe or serious or lasting ≥ 4 weeks)) according to recent revision of list of AESIs across the dupilumab program in AD.

2. INVESTIGATIONAL PLAN

2.1. Study Design and Randomization

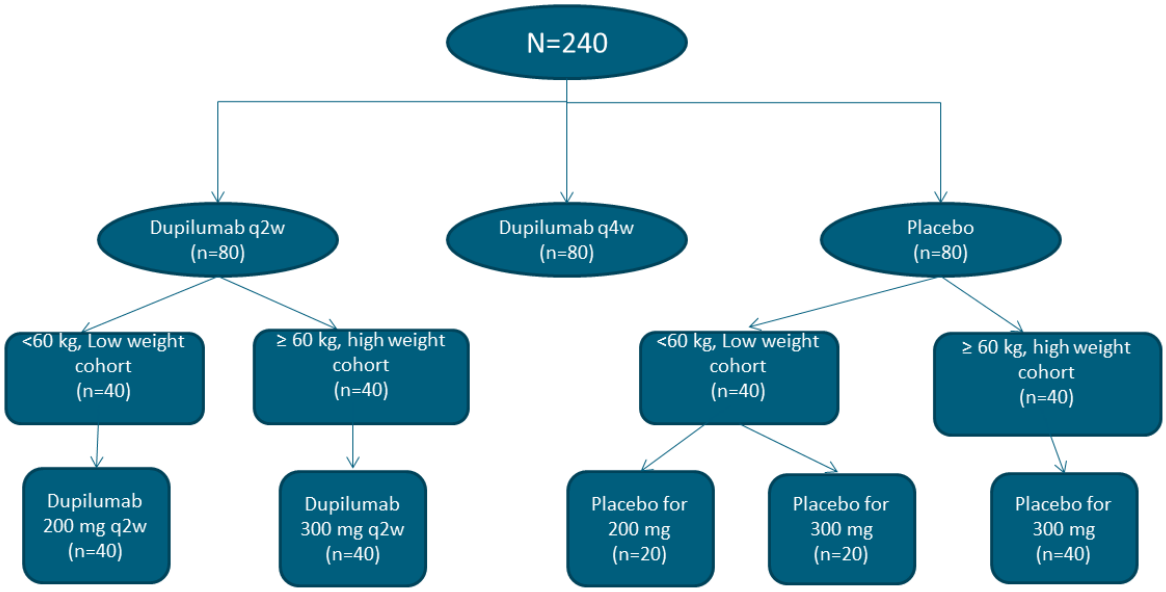
This is a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of dupilumab monotherapy in pediatric patients with moderate-to-severe AD. The study population will include patients ≥12 years to <18 years of age with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects or safety risks).

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio stratified by baseline weight group (<60 kg and ≥60kg; each weight stratum will enroll approximately 120 patients) and baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) as follows:

- Dupilumab Q2W treatment group: Patients with baseline weight <60 kg will receive Q2W subcutaneous (SC) injections of 200 mg dupilumab following a loading dose of 400 mg on day 1. Patients with baseline weight ≥60 kg will receive Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Dupilumab Q4W treatment group: Patients will receive Q4W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, irrespective of weight.
- Placebo treatment group: Patients will receive placebo matching dupilumab Q2W (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, patients in the <60 kg weight stratum will receive, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the patients randomized to the placebo group will receive placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

In order to maintain blinding, all patients will receive an injection Q2W from day 1 to week 14. Patients will receive placebo injection at the weeks dupilumab is not given.

Below diagram shows the planned number of patients in each dose group.



2.2. Sample Size and Power Considerations

Approximately 240 patients are planned to be randomized to 1 of the following treatment groups:

- Dupilumab Q2W treatment group: 200 mg Q2W patients <60 kg or 300 mg Q2W patients ≥60 kg
- Dupilumab Q4W treatment group: 300 mg Q4W
- Placebo group

It is estimated that with 80 patients per group, at the 2-sided 5% significance level, the study will have:

- 98% power to detect a difference of 28% between dupilumab Q2W treatment and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at week 16, assuming that the percentages are 37% and 9% for dupilumab Q2W and placebo, respectively.
- 88% power to detect a difference of 20% between dupilumab Q4W treatment and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at week 16, assuming that the percentages are 29% and 9% for dupilumab Q4W and placebo, respectively.
- 99% power to detect a difference of 35% between dupilumab Q2W treatment and placebo treatment in the percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 48% and 13% for dupilumab Q2W and placebo, respectively.
- 99% power to detect a difference of 32% between dupilumab Q4W treatment and placebo treatment in percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 45% and 13% for dupilumab Q4W and placebo, respectively.

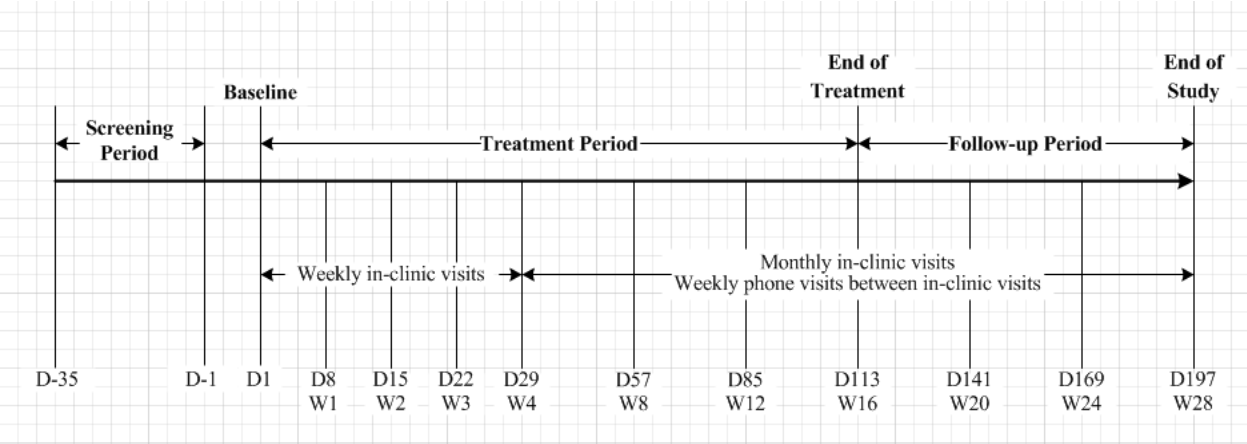
Additional power calculation based on the key secondary endpoint "proportion of patients with improvement (reduction) of Pruritus NRS ≥4 from baseline to week 16", with 80 patients per group, the study will provide:

- 97% power at a 0.05 level to detect a difference of 27% in the percentages of patients achieving Pruritus NRS reduction ≥4 at week 16, assuming that the percentages are 38% and 11% for dupilumab Q2W and placebo, respectively.
- 95% power at a 0.05 level to detect a difference of 25% in the percentages of patients achieving weekly average of daily peak Pruritus NRS reduction ≥4 at week 16, assuming that the percentages are 36% and 11% for dupilumab Q4W and placebo, respectively.

In the absence for data of dupilumab in pediatric patients with AD, the data observed in the adult studies R668AD-1334 and R668-AD-1416 studies (phase 3 studies for adult AD patients), and the R668AD1021 study (a phase 2b dose-ranging study in adults with AD) are used to generate the assumptions for these sample size calculations. Based on the result from the R668-AD-1021 study, the efficacy profile of dupilumab 200 mg Q2W is similar to dupilumab 300 mg Q2W.

2.3. Study Plan

The study will consist of the following 3 periods: screening of up to 5 weeks, treatment period of 16 weeks, and follow-up of 12 weeks as presented below:



Note: D = study day; W = study week

After the parents or legal guardians/patients provide an Informed Consent and Informed Assent (as appropriate), the patients will be assessed for study eligibility at the screening visit. During the screening period, systemic and topical treatments for AD will be washed out, as applicable, according to the eligibility requirements. Patients may be rescreened once if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure is related to failing the disease severity inclusion criteria. Patients will be required to apply moisturizers twice daily for at least 7 days before randomization and continue throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of nonlesional skin designated for such assessments for at least 8 hours before each clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio stratified by baseline weight group (<60 kg and ≥60kg; each weight stratum will enroll approximately 120 patients) and baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) as follows:

- Dupilumab Q2W treatment group: Patients with baseline weight <60 kg will receive Q2W SC injections of 200 mg dupilumab following a loading dose of 400 mg on day 1. Patients with baseline weight ≥60 kg will receive Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Dupilumab Q4W treatment group: Patients will receive Q4W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Placebo treatment group: Patients will receive placebo matching dupilumab Q2W (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, patients in the <60 kg weight stratum will receive, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the patients randomized to the placebo group will receive placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

In order to maintain blinding, all patients will receive an injection Q2W from day 1 to week 14. Patients will receive placebo injection at the weeks dupilumab is not given.

During the treatment period, patients will have weekly in-clinic visits through week 4, and then in-clinic visits every 4 weeks through week 16 with weekly telephone visits in between the in-clinic visits. Patients and/or parents/caregivers (as deemed appropriate based on age of patient) will be trained on injecting study drug during in-clinic visit 2 (day 1) to visit 6 (week 4). During weeks in which no in-clinic visit is scheduled, patients will either self-inject study drug or the parent/caregiver will administer study drug to the patient. In case patients do not want to self-inject and the parent/caregiver do not want to administer study drug to patient, patients may have the clinic staff administer all the study drug injections in the clinic. Safety, laboratory, and clinical assessments will be performed at specified clinic visits, as noted in schedule of event Appendix 10.2. The end of treatment period visit will occur at week 16, two weeks after the last dose of study drug. The co-primary endpoints will be assessed at this visit. If patients prematurely discontinue study treatment, the patients will be encouraged to stay in the study to have data collected at all remaining scheduled visits until completion of the planned end of study visit.

Patients who participate in the study may subsequently be eligible to participate in an open-label extension study.

Patients who complete this study (ie, up to the end of study visit at week 28) may be eligible to enroll in a subsequent extension study in which they will receive open-label treatment with dupilumab. In order to remain eligible for the open-label extension study, patients are required to adequately complete the assessments scheduled for the treatment period (through week 16) and follow-up period (week 20 through week 28), per the schedule of events.

As an exception to the above requirement, patients may be allowed to enroll into the open-label extension study earlier once they have completed the treatment period of this study (ie, at or after week 16), if they meet all of the following criteria:

- The patient needs to have completed at least 5 on site visits (including completing the study assessments and procedures planned for each of those visits) during the 16 week treatment period.

  AND

- The patient needs to have completed at least 6 study drug administrations during the 16-week treatment period.
- Patients have completed the week 16 visit (the protocol-defined "end of treatment" visit).
- Patients have completed the early termination visit. This visit may be conducted as early as week 16. The open-label extension screening visit may be completed on the same day as the early termination visit.
- Patients have an IGA ≥3 and BSA affected by AD lesions ≥10% at the early termination visit.
- Patients meet the eligibility criteria for the open-label extension study.
  Patients who have study drug permanently discontinued due to safety reasons will not be eligible to enroll in the open-label extension study.

  NOTE:

  – In case a patient experiences a flare of disease during the follow-up period and would otherwise require treatment with systemic corticosteroids or systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc), he/she can be enrolled directly into this open-label extension study at the investigator's discretion before completion of the entire follow-up period. However, it is required that an IGA be performed in this case and only patients who have an IGA ≥3 be considered for direct roll-over into this extension study.

  – Patients who turned 18 years of age during this study will not be eligible to enroll into the pediatric open-label extension study (R668-AD-1434). In case the drug is not commercially available for patients aged ≥18 years at the time the patient completes this study, these patients may be eligible for, and might have the opportunity to, enroll into the adult open-label extension study (R668-AD-1225), if the study is still ongoing.

  – Study drug administration refers to injections of dupilumab or placebo.

Patients who decline to enroll in the open-label extension study will be followed up for 12 weeks. For these patients, after week 16, 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 per schedule as noted in Appendix 10.2 (schedule of events).

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. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated at randomization (as randomized).

The per-protocol set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. A major efficacy-related protocol violation is one that may affect the interpretation of study results. The criteria of major efficacy-related protocol deviation are defined as following:

- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
  - Inclusion criteria 3, 4, 5, 6, 7, 8 and 9*
  - Exclusion criteria 1, 2*, 3*, 4, 5, 6*, 8, 9, 10,11, 19
- Patients who received <80% of the scheduled doses during the study treatment period

  *Note: Will be adjudicated on a case by case basis in blinded fashion prior to database lock

Final determination of the PPS will be made in a blinded manner prior to the database lock.

All efficacy variables will be evaluated on the FAS; the primary endpoint and key secondary endpoints will also be evaluated on the PPS. Analysis on the FAS will be considered to be primary.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive at least one injection 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 actual treatment group as treated is defined by the following rules:

- For a patient randomized to dupilumab (Q2W or Q4W), if the patient received all placebo injections, the actual treatment will be assigned as placebo.
- For a patient randomized to dupilumab (Q2W or Q4W), if the patient received at least one dupilumab injection, the actual treatment will be same as the planned treatment.
- For patients randomized to placebo but accidentally received dupilumab injections, the actual treatment will be assigned as dupilumab 300 mg Q4W.

In addition:

- Nonrandomized but treated patients will not be part of the safety population; 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:

- Week 16 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 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 SAF will be included, which is defined as the patients who entered the follow-up period and had at least one visit after week 16 treatment visit.

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. Patients will be analyzed according to the treatment actually received.

3.4. The ADA Analysis Set (AAS)

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

The neutralizing antibody (NAb) Analysis Set (NAS) will consist of all patients who received any study drug and who had at least one non-missing Nab result or who had all samples negative in the ADA assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

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 (≥15 to <18, ≥12 to <15), sex, ethnicity, race, baseline weight (kg) with grouping (<60 kg, >=60 kg), height (m), BMI (kg/m^2) with grouping (<20, >=20)
- Baseline characteristics: Duration of AD disease with grouping (< 13 years, >=13 years), Peak Pruritus numerical rating scale (NRS), Pruritus Categorical Scale (PCS), Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) affected by Atopic Dermatitis, Patient global assessment of disease status, Patient Oriented Eczema Measure (POEM), Children's Dermatology Life Quality Index (CDLQI), Global Individual Signs score (GISS), Hospital Anxiety and Depression Scale (HADS) total score, HADS-Anxiety subscale score, HADS-Depression subscale score, Asthma Control Questionnaire (ACQ-5), and Total Nasal Symptom Score (TNSS), Patients with inadequate response to topicals (Yes/No) with the reasons for patients who are "No" for inadequate response to topicals

4.2. Medical History and Atopic Disease Medical History

Medical history will be coded to a Preferred Term (PT), High Level Term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO. Information on conditions related to AD 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. 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, Azathiophrine and other treatments) during the last 6 months will also be collected.

4.3. Pre-treatment/Concomitant Medications and Procedures

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

Procedures will be coded to a Preferred Term (PT), High Level Term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO.

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

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug 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 week 16 visit date is missing. Medications/procedures taken during the 16 week treatment period and continued afterwards into 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
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic nonsteroid immunosuppressant (may be used as rescue)
- Treatment with systemic corticosteroids (may be used as rescue)
- Treatment with TCS or TCI (may be used as rescue)
- Treatment with crisaborole (may be used as rescue)
- Initiation of treatment of AD with prescription moisturizers

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Tanning in a bed/booth
- Phototherapy (UVA, UVB, nbUVB, high dose UVA and PUVA)

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. For the purpose of efficacy analysis, patients who receive rescue treatment during the study will be considered treatment failures. If possible, investigators are encouraged to consider rescue initially with topical treatment (eg, medium/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. Topical calcineurin inhibitors may be used for rescue, alone or in combination with TCS, but the use of TCIs should be reserved for problem areas only (eg, face, neck, intertriginous and genital areas, etc.). Patients who receive systemic corticosteroids or systemic non-steroidal immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) as rescue treatment 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 (eg, disease severity scores, safety laboratory tests) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication or procedure, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure. The rescue treatments will be adjudicated by the clinical study director and the adjudication procedure will be documented.

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 ex-US countries, 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 10.2.

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

The EASI will be collected at the scheduled and unscheduled clinic visits according to Appendix 10.2.

4.4.2. Secondary Efficacy Variables

The key secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for ex-US countries as it is already a co-primary endpoint)
- Percent change in EASI score from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline at week 16
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline at week 16

Peak Pruritus Numeric Rating Scale (NRS)

The Peak Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a 24-hour recall period. Patients will be asked the following questions:

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

Patients will be instructed on using the patient diary to record their Pruritus NRS score at the baseline visit. Patients will complete the rating scale daily throughout the entire study (screening period, treatment period, and follow-up period). Clinical sites will check and remind patients to complete the diary at each visit.

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

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

Other secondary endpoints are:

- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline during the 16-week treatment period

- Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline during the 16-week treatment period
- 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 CDLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Percent change from baseline to week 4 in weekly average of daily peak Pruritus NRS
- Change from baseline to week 16 in HADS
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 4
- Incidence of skin-infection TEAEs (excluding herpetic infections) through week 16*
- Incidence of serious TEAEs through week 16

*It will be adjudicated by study medical director.

Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.

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 10.2.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). The extent of AD is assessed by the Investigator as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms (erythema, oedema/papulation, excoriations, lichenification, oozing / crusts and dryness) of AD is assessed by the Investigator using the following scale:

- 0: None
- 1: Mild
- 2: Moderate
- 3: Severe

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.

Patients will undergo this assessment at the scheduled and unscheduled clinic visits according to Appendix 10.2.

Children's Dermatology Life Quality Index (CDLQI)

The CDLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on Quality of Life (QoL) in children. The format is a simple response to 10 items, which assess QoL over the past week. For each item, the scale is rated as follows:

- 0 = Not at all = Not relevant
- 1 = Only a little
- 2 = Quite a lot
- 3 = Very much = yes = prevent school

In question 7, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. For general inflammatory skin conditions a change in CDLQI score of at least 4 points is considered clinically important. The CDLQI will be assessed at the scheduled and unscheduled clinic visits according to Appendix 10.2.

Handling missing items from CDLQI:

a. 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.

b. If two or more questions are left unanswered the questionnaire is not scored.

c. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

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

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

Hospital Anxiety and Depression Scale (HADS)

The HADS is a tool widely used to detect states of anxiety and depression in a general hospital setting. The 14 items on the questionnaire, assessing how the patient has been feeling in the past week, include 7 items that are related to anxiety (odd numbered questions) and 7 items that are related to depression (even numbered questions). Questions 2, 4, 7, 9, 12, and 14 are scored from 0 (less distress) to 3 (greater distress) according to the content of the item. Questions 1, 3, 5, 6, 8, 10, 11, and 13 are reverse scored from 0 (greater distress) to 3 (less distress). A person can score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8–10 represents 'probable case' and 0 – 7 'not a case' (Zigmond 1983).

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

The questionnaire will be administered only to the subset of patients who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at time points according to Appendix 10.2.

4.4.3. Other Efficacy Variables

Other 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
- Patient global assessment of disease: proportion of patients with no symptom and proportion of patients with no symptom or mild symptoms at week 16
- Patient global assessment of treatment: proportion of patients who rate their eczema symptoms as "much better" at week 16
- Pruritus categorical scale: proportion of patients who achieve absence of pruritus or mild pruritus at week 16
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Change in ACQ-5 score from baseline at week 16
- Change in weekly averaged TNSS score from baseline at week 16
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Number of missed school days assessment during the treatment period
- Mean score of injection site pain as assessed by visual analogue scale for all visits through week 16

Patient Global Assessment of Disease

Patients will rate their disease based on a 5-point Likert scale. Patients will be asked: "Overall, how would you rate your eczema symptoms right now?" Response choices are:

- 1: No symptoms
- 2: Mild symptoms
- 3: Moderate symptoms
- 4: Severe symptoms
- 5: Very severe symptoms

Patients will undergo this assessment at time points according to Appendix 10.2.

Patient Global Assessment of Treatment

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale. Patients will be asked: "Compared to before you started the study, how would you rate your eczema symptoms now?" Response choices are:

- 1: Much better
- 2: A little better
- 3: No difference
- 4: A little worse
- 5: Much worse

Patients will undergo this assessment at time points according to Appendix 10.2.

Patient Assessment of Pruritus Using Pruritus Categorical Scale (PCS)

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in clinical studies of AD and has less of a "middling" effect (Kaufmann 2006). The scale is rated as follows:

- 0: Absence of pruritus
- 1: Mild, pruritus (occasional slight itching/scratching)
- 2: Moderate pruritus (constant or intermittent itching/scratching that does not disturb sleep)
- 3: Severe pruritus (bothersome itching/scratching that disturbs sleep).

Patients will be instructed on using the patient diary to record their pruritus categorical scale score at the baseline visit. Patients will complete the rating scale DAILY throughout the entire study (screening period, treatment period, and follow-up period). Clinical sites will check and remind patient to complete the diary at each visit.

For each day, if there are multiple PCS scores collected on the same day, the maximum (worst) of all the scores collected will be chosen. For each week, calculate round prorated average of collected scores for Category Score. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3 round to 1.0.

The baseline PCS is defined as the round prorated average of the PCSs reported right before and on the baseline visit (i.e. study day -6 to day 1).

Juniper Asthma Control Questionnaire (ACQ-5)

The 5-question (symptoms only) version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of asthma and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at time points according to Appendix 10.2.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ, any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing value, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

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. The GISS will be assessed at the scheduled and unscheduled clinic visits according to Appendix 10.2.

Total Nasal Symptom Score

The Total Nasal Symptoms score (TNSS) will be used to assess the effect of study drug on symptoms of allergic rhinitis. The TNSS total score will be the sum of the following 5 symptoms: rhinorrhea, nasal congestion, nasal itching, sneezing, and difficulty in sleeping, each rated on a 0 to 3 scale of severity. The modified TNSS total score will be the sum of 4 symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. Both TNSS total score and modified total score will be analyzed. The questionnaire will be administered only to the subset of patients with allergic rhinitis who fluently speak a language in which the questionnaire is presented (based on availability of translations in participating countries). Patients will be instructed on using the patient diary to record their TNSS score at the scheduled and unscheduled clinic visits according to Appendix 10.2.

The weekly averaged TNSS score will be calculated as the prorated average of the reported daily TNSS score within 7 days prior to the visit. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3.

Subgroup analysis of TNSS data for patients with perennial allergic rhinitis may be performed.

Injection Site Pain Visual Analogue Scale

Patients will be asked to provide an assessment of pain experienced during injection of study drug using a Visual Analogue Scale (VAS). This assessment will be performed after injection of the study drug at certain in-clinic visits according to Section 6.1.

4.5. Safety Variables

4.5.1. Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature and then 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, latest version).

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

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

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

The criteria for determining whether an abnormal laboratory, vital sign or 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 emergent period is defined as the period from the administration of first study dose to the EOS visit.

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

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during pre-treatment period.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only the 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 as 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 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 study.

Adverse event of special interest (AESI) category:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Malignancy (except in situ carcinoma of the cervix, non-metastatic squamous or basal cell carcinoma of the skin)
- Helminthic infections
- Suicide-related events
- Any type of conjunctivitis or blepharitis (severe or serious)
- Keratitis (any event regardless of severity or seriousness)

Appendix 10.54 provides a list of AESIs search criteria.

4.5.2. Laboratory Safety Variables

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

Samples for laboratory testing will be collected according to visit schedule (Appendix 10.2). 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

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Serum and urine pregnancy testing will be performed for all female patients of childbearing potential at time points according to Appendix 10.2. 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), and alcohol and drug screen test.

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)

Vital signs including temperature, sitting blood pressure, heart rate, and respiration, will be collected predose at every in-clinic visit. At the first 3 administrations of study drug (day 1, week 2 and week 4), sitting blood pressure, heart rate, and respiratory rate will also be assessed at 30 (±10) minutes postdose. See Appendix 10.2 for assessment time points.

4.5.4. Body Weight and Height

Body weight and height will be measured at time points according to Appendix 10.2.

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 visit schedule (Appendix 10.2).

4.6. Pharmacokinetic (PK) Variables

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Appendix 10.2. PK variables consist of functional dupilumab concentration and time (both actual and nominal).

4.7. Antibody (ADA) Variable

Serum samples for anti-dupilumab antibody will be collected at time points according to visit schedule (Appendix 10.2).

ADA variables include ADA response status and titer as follows:

- Total patients with preexisting immunoreactivity

  Pre-existing immunoreactivity defined as either an ADA positive response in the 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 over baseline titer levels

- Total patients with treatment emergent response

  Treatment emergent response is defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment emergent responses will 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 greater than 12-week period (greater than 84 days), with no ADA negative samples in between

  – Indeterminate Response - as a treatment-emergent response with only the last collected sample positive in the ADA assay

  – Transient Response - a treatment emergent ADA positive assay response that is not considered persistent or indeterminate.

- Total patients with treatment boosted response

  Treatment boosted response defined as a positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive

- Titer Values (Titer value category)

  – Low (titer <1,000)

  – Moderate (1,000 ≤ titer ≤ 10,000)

  – High (titer >10,000)

Samples positive in the ADA assay will be further characterized for ADA titers and for the presence of neutralizing antibody (NAb) response.

Total patients positive in the Neutralizing antibody assay
Treatment-emergent or treatment boosted ADA positive patients that are positive in the NAb assay at any time point analyzed.

4.8. Biomarkers Variables

Biomarkers to be analyzed in this study are:

- TARC
- Total serum IgE
- Immunoglubin 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 10.2.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, standard deviation, median, 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 3 treatment groups (i.e. dupilumab Q2W dose, dupilumab Q4W dose and placebo). All placebo patients will be pooled for analysis regardless if it is 200 mg placebo or 300 mg placebo.

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for FAS. Listing of demographics and baseline characteristics will be presented.

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.

Information on conditions related to AD 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. will be summarized.

5.3. Pre-treatment/Concomitant Medications/Procedures

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 groups. Patients will be counted only once for each medication class (ATC level 2 and 4) linked to the medication.

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 combined dupilumab treatment groups. Patients will be counted only once for each SOC and PT linked to the procedure.

Prior medications or procedures started before screening visit and started between screening visit and first injection date will be summarized separately.

Number and proportion of patients taking adjudicated rescue treatment (concomitant topical treatments (TCS/TCI), systemic immune-suppressants) and other treatments (emollients/ antihistamines) will also be summarized separately.

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

The compliance 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.

Listing of medications and procedures will be provided.

5.4. Subject Disposition

The following summaries by table will be provided:

- The total number of screened patients
- The total number of randomized patients: 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
- The total number of patients who completed the study treatment and discontinued the study treatment with the reason of discontinuation
- The total number of patients who continued in pediatric or adult open label extension study
- The total number of patients who entered into follow-up period and their study completion status with reason of discontinuation
- The total number of patients who entered into open-label extension study (OLE)

The following listings will be provided:

- Listing of patient disposition including: date of randomization, date of the last visit, received dose, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation
- Summary table with listing of protocol deviations will be provided

5.5. Dose administration

The compliance with study treatment 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%

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%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information, and whether or not the total dose is administered for each dose will be presented.

5.6. Treatment Exposure and Observation Period

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

(Date of last study drug injection – date of first study drug injection) + 14

The calculations are regardless of temporary dosing interruption. The duration of exposure during the study will be summarized by treatment group using number of patients, means, SD, minimums, medians, and maximums.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well:
≥ 14 days, ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥ 70 days, ≥ 84 days, ≥ 98 days, and ≥ 112 days.

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

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

The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest is specified as: < 8 days, ≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥50 days, ≥ 57 days, ≥ 85 days, ≥99 days, ≥113 days, ≥141 days, ≥169 days, ≥183 days and ≥197 days.

5.7. Analyses of Efficacy Variables

For all efficacy variables, the analysis will be comparisons of each dupilumab regimen and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested for each dupilumab regimen group and the placebo group:

H0: $p_{dupilumab} = p_{placebo}$, where p stands for the percent of responders in a treatment group

H1: $p_{dupilumab} \neq p_{placebo}$.

The analyses of efficacy variables are described in the subsections below and summarized in Appendix 10.1.

Subgroups are defined by key baseline factors recorded on the CRF and listed to be considered for primary and key secondary efficacy analyses:

- Age group (≥12 to <15, ≥15 to <18)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black or African American, Asian, Other)
- Duration of AD (< 13 years, ≥13 years)
- Age of disease onset (<2 years, ≥2 years)
- Age of disease onset (<5 years, ≥5 years)

- Family history of atopic disease (Yes/No)
- Baseline weight group (<60 kg, ≥60 kg)
- Baseline BMI group (overweight: >= 85 percentile of general population based on age and gender, < 85 percentile)

  Baseline disease severity [moderate (IGA=3) and severe (IGA=4)]
- Baseline severe EASI (<25, ≥25)
- Baseline NRS (<7, ≥7)
- Body Surface Area (BSA) (≥10% - <30%, ≥30% - <50%, ≥50%)
- Previous usage of ciclosporin (CsA) (Yes, No)
- Previous usage of methotrexate (MTX) (Yes, No)
- Previous use of systemic immunosuppressants for AD (Yes, No)
- History of asthma (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergies (Yes, No)

5.7.1. Analysis of Primary Efficacy Variable

The Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (disease severity (IGA=3 or 4), weight group (<60 kg or ≥60kg)) will be used for the analysis of percentage of patients with IGA 0 or 1 at week 16 or percentage of patients with EASI-75 at week 16.

All efficacy data, regardless of the patient being on the study treatment or discontinues the study treatment but remains in the study, will be used for analysis. Specifically, if a patient stays in the study until the end of the study planned placebo-controlled treatment period, all efficacy data collected up to the study planned end of treatment visit will be included in the primary analysis, regardless if the patient is on treatment or not.

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

- If a patient withdraws from the study, 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 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, then it will be counted as a non-responder at week 16.

The Mantel-Fleiss (MF) criterion will be performed, and if it is not met while using the option CMH (MF) in SAS procedure PROC PREQ, sensitivity analyses including each factor separately in CMH test will be conducted.

Sensitivity analyses

1. Post-baseline Last Observation Carried Forward (LOCF) approach after censoring for rescue treatment use or study withdrawal to determine patient's status at week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data.
2. All observed data, regardless if rescue treatment is used or data is collected after withdrawal from study treatment will be included for analysis. Patients with missing value will be counted as non-responder.

The primary efficacy analyses will be performed on FAS, as well as on PPS as a supporting analysis.

5.7.2. Analyses of Secondary Efficacy Variables

The binary secondary efficacy endpoints will be analyzed using the same approaches as that are used for the analysis of the primary endpoints.

The endpoint "Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 16" will only be analyzed for patients with baseline peak pruritus NRS ≥4. Similarly the endpoint "Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥3 from baseline to week 16" will only be analyzed for patients with baseline peak pruritus NRS ≥3.

The continuous endpoints will be analyzed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model as the primary analysis method. Patients' efficacy data through week 16 after the rescue treatment use will be set to missing first, and then be imputed by the multiple imputation method. 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. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, randomization strata (disease severity, age group), and relevant baseline.

The week 16 data of each of the 40 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (disease severity, age group), 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 (disease severity, weight group)
- Measured endpoint values at every clinic visit (i.e. week 1, 2, 3, 4, 8, 12 and week 16)

Categorical variables included in above model (i.e., treatment group and randomization strata) are not expected to be missing.

To account for the impact of rescue treatment on the efficacy effect:

- Continuous efficacy endpoints: if a patient receives rescue treatment that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue treatment is initiated will be treated as missing.

Sensitivity analyses

In addition to the MI method described previously, sensitivity analyses for the continuous endpoints for EASI and/or Pruritus NRS will be conducted as described below.

1. The sensitivity analysis based on all observed data regardless if rescue treatment is used or data is collected after withdrawal from study treatment using MI method will be performed.
2. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue treatment is used. The post-baseline LOCF method will then be used to impute missing values.
3. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue treatment is used. The post-baseline worst observation carried forward (WOCF) method will then be used to impute missing values.

Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS >=4 from baseline during the 16-week treatment period will be calculated for each patient as (the date of having the first event - the first study drug dose date + 1 day. Patients not having any event during the treatment period will have their time censored at the end of treatment period. Time to onset of effect on pruritus will be analyzed using the Cox proportional hazards model including treatment and randomization strata as factors. The hazards ratio, its 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be provided.

Analysis of incidence of TEAE-related variables

- Incidence of skin infection TEAE (excluding herpetic infections) from baseline through week 16
- Incidence of treatment-emergent serious adverse events from baseline through week 16

These endpoints will be analyzed for patient in SAF. The week 16 treatment period is defined in Section 3.2. The Cochran-Mantel-Haenszel test adjusted for randomization strata will be used for the percentage of patients with events described above through week 16.

Multiplicity Considerations

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-I error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens 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).

	Endpoints	**Dupilumab**	
		Q4W group	**Q2W group**
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	10	1
Co-primary endpoint for ex-US countries, key secondary for US	Proportion of patients with EASI-75 (>=75% improvement from baseline) at week 16	9	2
Key Secondary endpoints	Percent change in EASI score from baseline to week 16	11	3
	Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS	12	4
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS >=3 from baseline to week 16	13	5
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS >=4 from baseline to week 16	14	6
Secondary endpoints	Proportion of patients with EASI-50 at week 16	15	7
	Proportion of patients with EASI-90 at week 16	16	8
	Time to onset of effect on pruritus during the 16-week treatment period (≥3 point reduction of weekly average of peak Pruritus NRS from baseline)	25	17
	Time to onset of effect on pruritus during the 16-week treatment period (≥4 point reduction of weekly average of peak Pruritus NRS from baseline)	26	18
	Change from baseline to week 16 in percent BSA affected by AD	27	19
	Percent change from baseline to week 16 in SCORAD	28	20
	Change from baseline to week 16 in CDLQI	29	21
	Change from baseline to week 16 in POEM	30	22
	Change from baseline to week 16 in weekly average of daily peak Pruritus NRS	31	23
	Percent change from baseline to week 4 in weekly average of daily peak Pruritus	32	24
	Change from baseline to week 16 in HADS	35	33
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS >=4 from baseline to week 4	36	34
	Incidence of skin-infection TEAEs (excluding herpetic infections) through week 16	39	37
	Incidence of serious TEAEs through week 16	40	38

5.7.3. Subgroup Analysis

Subgroup for the primary endpoint and key secondary efficacy will be analyzed based on FAS. The analysis method for the subgroup will be the same as the primary analysis described in Section 5.7.1 and Section 5.7.2. Interactions between the subgroups and treatment groups will also be tested using the logistic regression model for the categorical endpoints, and using the ANCOVA model for the continuous endpoints. The model will include randomization strata, treatment group, subgroup, and treatment by subgroup interaction as factors. P-values for the interaction term will be reported.

Forest plots of the primary and key secondary efficacy endpoints across subgroups will be generated.

5.7.4. Analyses of Other Efficacy Variables

The analyses of other efficacy variables will be the same as the primary analysis described in Section 5.7.1 and Section 5.7.2.

5.8. Analysis of Safety Data

The summary of safety and tolerability will be performed based on 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 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

Subgroups are defined by key baseline factors recorded on the CRF and listed to be considered for safety analyses:

- Age group (≥12 to <15, ≥15 to <18)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino (no/yes))
- Race (White, Black, Asian, Other)
- Duration of AD (< 13 years, ≥13 years)
- Baseline BMI group (overweight: >= 85 percentile of general population based on age and gender, < 85 percentile)
- Baseline weight group (<60 kg, ≥60 kg)

5.8.1. Adverse Events

Listings of TEAEs, serious TEAEs, and TEAEs resulting in death and study drug discontinuation will be generated.

Number and proportions of patients reporting TEAEs will be summarized for 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 based on the overall incidence for the combined dupilumab treatment groups.

Summaries of TEAEs will include:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - Common TEAEs by SOC/HLT/PT (incidence with PT ≥5%)
  - Common TEAEs by SOC/HLT/PT (incidence with PT ≥2%)
  - 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/HLT/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
- Death by SOC/PT
- AESI by AESI category (see Appendix 10.5) and SOC/PT

The time to first AESIs (TEAE category), serious TEAE, or TEAE leading to permanent treatment discontinuation during the treatment period 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 treatment period.

5.8.2. 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 patients with abnormal lab value during study whose screening and baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs overall during the study, during the treatment period and during the follow-up period
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by patient and visit will be provided.

5.8.3. 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

Listings of vital sign will be provided with flags indicating the treatment-emergent PCSVs.

5.8.4. 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. A summary of treatment-emergent abnormal findings will be provided.

5.8.5. 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

Listings of ECG will be provided with flags indicating PCSVs.

5.9. Analysis of Pharmacokinetic Data

The following analyses will be conducted:

- Descriptive statistics of functional dupilumab serum concentrations 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.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

The incidence of ADA variables described in Section 4.7 will be summarized using absolute occurrence (n) and percent of patients (%) with pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent ADA responses and titer categories by treatment groups. Listing of all ADA peak titer levels will be provided for ADA positive subjects.

5.10.2. Analysis of Neutralizing Antibodies (NAb)

The absolute occurrence (n) and percent of patients (%) with Nab positive or negative status will be provided by treatment group for patients in the NAb analysis set.

5.11. Association of Immunogenicity with Exposure, Safety and Efficacy

5.11.1. Immunogenicity and Exposure

Associations between key ADA variables and systemic exposure to dupilumab may be explored for the dupilumab treated patients. Plots of dupilumab concentration may be provided for analyzing the potential impact of treatment-emergent, persistent and titer ADA responses (high, moderate or low) on PK.

5.11.2. Immunogenicity and Safety and Efficacy

Associations between the ADA response and safety events may be explored.

Associations between the ADA variables and key efficacy endpoints may be explored for the dupilumab treated group. Plots of efficacy variables may be analyzed for potential impact of treatment-emergent ADA on efficacy.

The above mentioned safety and efficacy analyses 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 had positive in the NAb assay at any time point analyzed.
- Peak post-baseline titer level in treatment emergent or treatment boosted ADA positive patients:
  - High,
  - Moderate,
  - Low

5.12. 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, IgG subclasses)
- antigen-specific IgE
- Lactate dehydrogenase (LDH)

The Wilcoxon signed-rank test stratified by the baseline disease severity 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 on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group and the baseline disease severity as fixed effects, and the relevant baseline values as covariate. Missing value will be imputed by LOCF method for visits between post-baseline to week 16. After week 16, no imputation will be made. P-value for difference from placebo will be provided.

Correlation of baseline TARC (measured value) and IgE (measured value), absolute change or percent change from baseline value of baseline TARC (measured value) and IgE (measured value) with the following clinical endpoints will be explored using the Spearman's rho test. Both Spearman correlation coefficients and p-value will be reported.

- Percent change from baseline to week 16 in EASI score
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD

Correlation of baseline TARC (measured value) and IgE (measured value) with the following clinical endpoints will be explored using the ANOVA model. The model includes the baseline biomarker data as the dependent variable, and treatment group, the responder/nonresponder of below clinical endpoint as the predictor variable. P-value will be provided to indicate significance of the responder/non-responder factor.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16

Association of positivity to at least one antigen-specific IgE with the following clinical endpoints will be explored using CMH test stratified by the baseline disease severity. The risk ratio and p-value from the chi squared test will be provided.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16

Correlation/association will be implemented on the placebo, dupilumab Q2W, dupilumab Q4W and combined dupilumab (dupilumab Q2W and Q4W) groups, respectively.

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 are established clinical assays; the upper limit of normal (ULN) from the central lab reference range will determine the threshold for normal vs. elevated status.

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 NRS 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 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 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 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 to in line with the protocol which specifies to collect up to 2 years 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 post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.4. Analysis Visit Window

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

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

Visit	Target Day	Analysis Time Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 1	8	[2,11]
Week 2	15	[12,18]
Week 3	22	[19,25]
Week 4	29	[26, 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 day is calculated relative to the date of first study drug injection.

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

1. Scheduled visit
2. Early termination (ET) or end of study (EOS), whichever comes first if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ET/EOT/EOS are not available

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

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

- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

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

Step 1: Derive the study day

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

Step 2:

- Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc., with 7 days interval between visit windows.

For TNSS data, the analysis visit windows will be implemented following the procedure below:

	Analysis visit window
Baseline	[Date of Visit 2 – 6, Date of Visit 2]
Week 4	[date of Visit 6 - 6, Date of Visit 6]
Week 16	[date of Visit 18 - 6, Date of Visit 18]
Week 28	[date of Visit 21 - 6, Date of Visit 21]

7. INTERIM ANALYSIS

No interim analysis is planned.

A first-step 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 first-step analysis. The assessment of primary and secondary endpoints performed during the analysis will be the final analysis of the primary endpoint and secondary endpoints. Hence, there will be no need for alpha adjustment due to the first-step 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 first-step analysis, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the first-step 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 9.2 or above.

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Parameter(s)	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
Investigator's Global Assessment (IGA)	• IGA 0 to 1 • reduction of ≥2 points from baseline	• CMH test adjusted by randomization strata	Yes for IGA 0 to 1, Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes for IGA 0 to 1,
Eczema Area and Severity Index (EASI)	• EASI 75 • EASI 50 • EASI 90 • % change from baseline • Change from baseline	• CMH test adjusted by randomization strata for categorical variables • Multiple imputation (MI) with ANCOVA for continuous variables	Yes for EASI-75 and % change, MMRM, ANCOVA for continuous variable, CMH on OC or LOCF for categorical variable	Yes for EASI-75 and % change
Pruritus Numeric Rating Scale (NRS)	• % change from baseline • reduction of ≥4 points from baseline • Change from baseline	• CMH test adjusted by randomization strata for categorical variables • Multiple imputation (MI) with ANCOVA for continuous variables	Yes for % change and reduction >=4	Yes for % change and reduction >=4
Pruritus Categorical Scale (PCS)	• Number (%) of patients	• CMH test adjusted by randomization strata	No	No
Body Surface Area (BSA) Involvement of Atopic Dermatitis	• % change from baseline • Change from baseline	• Multiple imputation (MI) with ANCOVA	No	No
SCORing Atopic Dermatitis (SCORAD)	• % change from baseline • Change from baseline • SCORAD50 • SCORAD75 • SCORAD90	• Multiple imputation (MI) with ANCOVA for continuous variables • CMH test adjusted by randomization strata for categorical variables	No	No

Parameter(s)	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
Global Individual Signs Score (GISS)	• % change from baseline • Change from baseline	• Multiple imputation (MI) with ANCOVA for continuous variables	No	No
Patient Oriented Eczema Measure (POEM)	• % change from baseline • Change from baseline	• Multiple imputation (MI) with ANCOVA for continuous variables	No	No
Children Dermatology Life Quality Index (CDLQI)	• Change from baseline	• Multiple imputation (MI) with ANCOVA for continuous variables	No	No
Hospital Anxiety and Depression Scale (HADS)	• % change from baseline • Change from baseline	• Multiple imputation (MI) with ANCOVA for continuous variables	No	No
Patient Global Assessment of Disease Status	• Number (%) of patients with no symptom • Number (%) of patients with no symptom or mild symptoms	• CMH test adjusted by randomization strata	No	No
Patient Global Assessment of Treatment	• Number (%) of patients who rate their eczema symptoms as “much better”	• CMH test adjusted randomization strata	No	No
Assess sick-leave/missed school days	• Number (%) of patients	• Descriptive statistics by visit/time	No	No
TNSS	• Change from baseline	• Multiple imputation (MI) with ANCOVA for continuous variables	No	No
VAS score of injection site pain	• Mean value	• Descriptive statistics	No	No

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	Yes for selected AE summary	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Events

Table 1: Schedule of Events – Screening, Baseline and Treatment Periods

	Screening	Treatment Period												
		BL												
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	PV7[d]	PV8[a]	PV9[a]	V10	PV11[a]	PV12[a]	PV13[a]	V14
Week (W)			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Study Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Window in days			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Screening/Baseline:														
Informed consent/assent	X													
Informed consent/assent for optional genomic sub-study[b]	X													
Medical history	X													
Demographics	X													
Inclusion/exclusion criteria	X	X												
Randomization		X												
Patient ediary training for pruritus assessments, TNSS assessment, and emollient use[c]	X	X												
Treatment:[a]														
Injection training/observation[e]		X		X		X				X				X
Study drug administration		X[f]		X[f]		X[f]		X		X		X		X
Patient/parent(s) or caregiver paper diary training for dosing						X								
Patient dosing diary completion								X				X		
Study drug dispensation[g]						X				X				X
Study drug accountability [g]										X				X
Review home ediary		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Treatment Period												
		BL												
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	PV7[a]	PV8[a]	PV9[a]	V10	PV11[a]	PV12[a]	PV13[a]	V14
Week (W)			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Study Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Window in days			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
medications/procedures														
Efficacy:[d]														
Patient assessment of pruritus intensity using NRS via diary (daily)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient assessment of pruritus intensity using PCS via diary (daily)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment of disease[h]	X	X		X		X				X				X
Patient global assessment of treatment[h]				X		X				X				X
[h] Patient-reported CDLQI[i], POEM[i], HADS[i]	X	X		X		X				X				X
[h] Patient-reported ACQ-5[i, j]	X	X												
Patient-reported TNSS[h, i, k]		X				X								
Patient assessment of injection pain using VAS[h]		X		X		X				X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X	X	X				X				X
Assess missed school days		X				X				X				X
Photograph AD areas (select sites)		X												
Safety:[d]														
Weight	X	X												
Height	X													
Vital signs	X	X[f]	X	X[f]	X	X[f]				X				X
Physical examination	X													
ECG	X													
Adverse events	X	X[f]	X	X[f]	X	X[f]	X	X	X	X	X	X	X	X

	Screening	Treatment Period												
		BL												
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	PV7[a]	PV8[a]	PV9[a]	V10	PV11[a]	PV12[a]	PV13[a]	V14
Week (W)			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Study Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Window in days			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Laboratory Testing: [d]														
Hematology	X	X				X				X				
Chemistry[m]	X	X				X				X				
Urinalysis[m]	X	X				X								
Alcohol & drug screen test	X													
Pregnancy test, WOCBP only	Serum	Ur	Ur	Ur	Ur	Ur				Ur				Ur
HIV, HBsAg, HBsAb, HBcAb, Hep C Ab, TB[l]	X													
Biomarker: [d]														
TARC	X	X		X		X				X				X
Total serum IgE, immunoglobulin profiling, antigen specific IgE	X	X				X				X				X
Biomarker samples (serum/plasma)		X				X				X				
Optional Genomics Study: [d]														
Optional DNA and RNA (whole blood) sample [b]		X												
Drug Concentration and ADA: [d]														
Functional dupilumab concentration sample		X		X		X				X				X
ADA sample		X				X								

BL = baseline; Ur = urine; WOCBP = women of childbearing potential; TB = tuberculosis

[a] The site will contact the patient/caregiver by telephone to conduct these visits. The patient/caregiver may administer study drug during phone visits. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and to document any related issues.

[b] For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

[c] Training of patients regarding completion of diary to record (1) completion of assessment of Pruritus NRS scale, (2) completion of assessment of Pruritus Categorical Scale, (3) completion of assessment of Total Nasal Symptoms Score (TNSS), and (4) emollient usage.

[d] Assessments/procedures should be conducted in the following order: patient reported outcomes(other than patient assessment of injection pain), investigator assessments, safety and laboratory assessments (including sample collection for ADA, PK, biomarker, and optional DNA and RNA), and administration of study drug. PK and ADA samples to be collected prior to the administration of the drug.

[e] Patients or parents/caregivers will be trained on how to administer study drug. This will enable administration at home in between clinic visits.

[f] Patients will be monitored at the study site at visits 2, 4, and 6 for a minimum of 30 minutes after study drug administration. Vital signs (sitting blood pressure, heart rate, and respiratory rate) and AEs will be assessed at 30 minutes (±10 minutes) post-injection.

[g] Starting at visit 6, study drug will be dispensed to the patients or parents/caregivers for the dose that will be administered before the next clinic visit. Patients or parents/caregivers will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. At these in-clinic visits, sites will perform accountability assessment for the study drug that the patients or parents/caregivers have returned to the site.

[h] Patient-reported assessments are to be completed only by the patient.

[i] The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).

[j] ACQ-5 will be administered only to patients with ongoing asthma.

[k] TNSS will be administered only to patients with medical history of allergic rhinitis throughout the screening period (at least 7 days before baseline/day 1) and only for 7 days preceding visit 6.

[l] Tuberculosis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.

[m] If baseline/day 1 visit occurs within 14 days of screening, hematology and serum chemistry do not need to be repeated at the baseline/day 1 visit as long as these assessments were performed at the screening visit

Table 2: Schedule of Events (Treatment Period cont, Follow-Up Period, Unscheduled Visits, and Early Termination)

Study Procedure	Treatment Period				Follow-Up Period[i]			Unscheduled Visit[b]	Early Termination Visit
				EOT[i]			EOS		
In-clinic Visit (V)	PV15[a]	PV16[a]	PV17[a]	V18	V19	V20	V21		
Week (W)	W13	W14	W15	W16	W20	W24	W28		
Study Day (D)	D92	D99	D106	D113	D141	D169	D197		
Window in days	±3	±3	±3	±3	±4	±4	±4		
Treatment:[c]									
Study drug administration		X							
Patient dosing paper diary completion		X							
Study drug accountability [d]				X				X	X
Review home ediary	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X
Efficacy:[c]									
Patient assessment of pruritus intensity using NRS via diary (daily) [e]	X	X	X	X	X	X	X	X	X
Patient assessment of pruritus intensity using PCS via diary (daily) [e]	X	X	X	X	X	X	X	X	X
Patient global assessment of disease [e]				X	X	X	X	X	X
Patient global assessment of treatment [e]				X	X	X	X	X	X
[e] Patient-reported CDLQI[f], POEM[f], HADS[f]				X	X	X	X	X	X
[e] Patient-reported ACQ-5 [g]				X			X		X
Patient-reported TNSS [e, f, h]				X			X		
Patient assessment of injection pain using VAS[h]									
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
Assess missed school days				X	X	X	X	X	X
Photograph AD areas (select sites)				X			X		X
Safety:[c]									
Weight				X			X		X
Height				X			X		X
Vital signs				X	X	X	X	X	X
Physical examination				X			X	X	X
ECG				X			X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Study Procedure	Treatment Period				Follow-Up Period[i]			Unscheduled Visit[b]	Early Termination Visit
				EOT[i]			EOS		
In-clinic Visit (V)	PV15[a]	PV16[a]	PV17[a]	V18	V19	V20	V21		
Week (W)	W13	W14	W15	W16	W20	W24	W28		
Study Day (D)	D92	D99	D106	D113	D141	D169	D197		
Window in days	±3	±3	±3	±3	±4	±4	±4		
Laboratory Testing:[c]									
Hematology				X			X	X	X
Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy test, WOCBP only				Urine			Urine	Urine	Urine
Biomarker: [c]									
TARC				X			X	X	X
Total Serum IgE, immunoglobulin profiling, antigen specific IgE				X			X	X	X
Biomarker samples (serum/plasma)				X					
Drug Concentration and ADA Samples: [c]									
Functional dupilumab concentration sample				X			X	X	X
ADA sample				X			X	X	X

EOT = End of Treatment; EOS = End of Study

[a] The site will contact the patient/caregiver by telephone to conduct these visits. The patient/caregiver may administer study drug during phone visits. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and to document any related issues.

[b] Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason (eg, before a rescue medication/procedure is used), as warranted.

[c] Assessments/procedures should be conducted in the following order: patient reported outcomes(other than patient assessment of injection pain), investigator assessments, and safety and laboratory assessments (including sample collection for ADA, PK, and biomarkers). Samples positive in the ADA assay will be analyzed in the neutralizing antibody (NAb) assay. PK and ADA samples to be collected prior to the administration of the drug.

[d] Patients or parents/caregivers will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. At these in-clinic visits, sites will perform accountability assessment for the study drug that the patients or parents/caregivers have returned to the site.

[e] Patient-reported assessments are to be completed only by the patient.

[f] The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).

[g] ACQ-5 will be administered only to patients with ongoing asthma.

[h] Total Nasal Symptoms Score will be administered only to patients with medical history of allergic rhinitis for 7 days preceding visit 18 and visit 21.

i The follow-up period will be for those patients who decline to enter the open-label extension study.

10.3. Criteria for Treatment-Emergent Potentially Clinical Significant Value for Pediatric Patients

Parameter	Treatment Emergent PCSV[1]	Comments
Clinical Chemistry		
ALT	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
AST	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin	≥1.3 ULN and baseline < 1.3 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Based on normal range: <1 mg/dL, CF = mg x 1.7 = µmol Concept paper on DILI – FDA draft Guidance Oct 2007.
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin ≥1.3 ULN)	Conjugated bilirubin will be measured when the total bilirubin is above the ULN Based on normal range: 0 to 0.4 mg/dL
ALT and Total Bilirubin	(ALT≥3 ULN and TBILI≥2 ULN) and baseline (ALT <3 ULN or TBILI <2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK	≥3 ULN and baseline < 3ULN	FDA Feb 2005. Am J Cardiol April 2006.
Creatinine	≥132µmol/L and baseline < 132µmol/L (or ≥1.5 mg/dL and baseline <1.5 mg/dL) >=30% change from baseline	Benichou C., 1994 Two independent criteria

[1] The ULN is based upon central lab reference ranges. The reference range might be different for different age-groups. For the purpose of this study in a particular patient the reference range based upon age at baseline will be used as reference throughout the study for determining PCSVs

Parameter	Treatment Emergent PCSV[1]	Comments
Uric Acid		
Hyperuricemia	>8.0 mg/dL and ≤8.0 mg/dl at baseline (or >476 µmol/L and ≤476 µmol/L at baseline	
Hypouricemia	≤2 mg/dL and >2 mg/dL at baseline (or ≤119 µmol/L and baseline > 119 µmol/L)	
Blood Urea Nitrogen	≥20 mg/dL and <20 mg/dL at baseline (or >=7.14 mmol/L and <7.14 mmol/L at baseline)	
Chloride		Two independent criteria
Hypochloremia	<80 mmol/L and baseline ≥ 80 mmol/L	Reference ranges are same in adolescents (12-17 yrs. old) and adults
Hyperchloremia	≥115 mmol/L and baseline < 115 mmol/L	
Sodium		Two independent criteria
Hyponatremia	<129 mmol/L and baseline ≥ 129 mmol/L	Reference ranges are similar in adolescents (12-17 yrs. old) and adults
Hypernatremia	≥150 mmol/L and baseline <150 mmol/L	
Potassium		FDA Feb 2005.
Hypokalemia	≤3.5 mmol/L and baseline >3.5 mmol/L	Two independent criteria
Hyperkalemia	≥5.5 mmol/L and baseline <5.5 mmol/L	Reference ranges are similar in adolescents (12-17 yrs. old) and adults
Calcium total	<2 mmol/L and baseline ≥2 mmol/L (or ≤ 8 mg/dL and baseline >8 mg/dL) ≥2.9 mmol/L and baseline <2.9 mmol/L (or ≥11.6 mg/dL and baseline <11.6 mg/dL)	
LDL Cholesterol	≥4.91 mmol/Land <4.91 mmol/L at baseline (≥ 190 mg/dl and <190 mg/dl at baseline)	Threshold for therapeutic intervention with pharmacotherapy in children (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011).
Total cholesterol	≥6.20 mmol/Land < 6.20 mmol/L at baseline (or ≥ 240 mg/dL and < 240 mg/dL at baseline)	
Triglycerides	Fasting level ≥ 5.64 mmol/Land < 5.64 mmol/L at baseline (or ≥ 500 mg/dL and < 500 mg/dL at baseline)	Threshold for therapeutic intervention with pharmacotherapy in children. (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011). CF = g x 1.14 = mmol
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)	

Parameter	Treatment Emergent PCSV[1]	Comments
HbA1c	>6.5% and <= 6.5% at baseline	WHO 2006/2011 ADA 2003 and 2012
Albumin	≤25 g/L and >25 g/L at baseline	Reference ranges are same in children (6-17 yrs. old) and adults
Hematology		
WBC	<4.0 Giga/L and ≥4.0 Giga/L at baseline >13.5 Giga/L and ≤13.5 Giga/L at baseline	
Lymphocytes	<0.6 Giga/L and ≥0.6 Giga/L at baseline >6.0 Giga/L and ≤6.0 Giga/L at baseline	
Neutrophils	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>1.2 Giga/L and <= 1.2 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	<10 g/dL and >10 g/dL at baseline (or <100 g/L and >=100 g/L at baseline) ≥20 g/dL and <20 g/dL at baseline (or >=200 g/L and <200 g/L at baseline)	Two criteria are independent
Hematocrit	For males: <0.37 v/v and ≥0.37 v/v at baseline; >0.52 v/v and ≤0.52 v/v at baseline For females: <0.33 v/v and ≥0.33 v/v at baseline <0.47 v/v and ≥0.47 v/v at baseline	Two Criteria are independent
Platelets	<100 Giga/L and ≥100 Giga/L at baseline >700 Giga/L and ≤ 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria

Parameter	Treatment Emergent PCSV[1]	Comments
Urinalysis		
Ketonuria	Presence and absence at baseline	Semi-quantitative methods
Glycosuria	Presence and absense at baseline	Semi-quantitative methods
Microscopic Hematuria	> 5 RBCs/ HPF and ≤5 RBCs/ HPF at baseline	Semi-quantitative methods
Proteinuria	≥ 1+ and <1 at baseline	Semi-quantitative methods, ≥ 1+ means concentration >=30 mg/dL
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	
SBP	Hypotension: SBP<5th percentile for gender, age and height; baseline >=5th percentile **and** decrease from baseline ≥20 mmHg	Based on definition of hypotension as SBP<5th percentile for gender, age and height
	Hypertension: At or above the 95th percentile for age, sex and height postbaseline; baseline < 95% percentile; **and** increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions
DBP	Hypotension: DBP<5th percentile for gender, age and height; baseline >=5th percentile and decrease from baseline ≥10 mmHg	Based on definition of Hypertension as average DBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions
	Hypertension: At or above the 95th percentile for age, sex and height postbaseline; baseline < 95% percentile and increase from baseline ≥10 mmHg	
Temperature	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary: >99 °F/37.2 °C	
Respiratory rate	<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline	
Weight	≥5% decrease 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.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥200 ms and < 200 ms at baseline	
QRS	≥110 ms & < 110 ms at baseline	

Parameter	Treatment Emergent PCSV[1]	Comments
QTc	Absolute values (ms) Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female	Bazett's formula (measured QT interval divided by the square root of the R-R) to be applied to arrive at corrected QT value interval)
	Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female	QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. independent criteria
	Additional: ≥500 ms and < 500 ms at baseline	
	Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	

10.4. Search Criteria for TEAE of Special Interest/TEAE Syndrome[1]

AESI	Search Criteria
Anaphylactic reactions	For SMQ "anaphylactic reaction" An **algorithmic approach** will be used. A case must include either: 1. A narrow term (a term from Category **A**); 2. Patient with both a term from Category **B** AND a term from Category **C**; 3. Patient with a term from Category **D** AND { a term from Category **B** - OR a term from Category **C** } For bullets 2 and 3, the search terms that are included under the SMQ for a particular event need to have the same start date (for e.g. if search shows cough (category B term) occurring at day 3 and urticaria (category C term) occurring at day 7, this event is not adjudicated as anaphylactic reaction as this is inconsistent with the clinical presentation of anaphylaxis as an acute event with simultaneous involvement of 2 or more body systems. Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Systemic or severe hypersensitivity reactions	Hypersensitivity: Narrow SMQ for hypersensitivity excluding preferred term equal to dermatitis atopic or eczema For systemic hypersensitivity, events in which 2 or more body systems are involved (as defined by System Organ Class) would be considered for adjudication based on further medical judgement For severe hypersensitivity, an additional search will be done; - HLT = Injection site reactions - Severity = "severe" Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Malignancy	• SMQ "Malignant tumours" • SMQ "Tumours of unspecified malignancy"
Helminthic infections[2]	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection
Suicidal behavior	Include the following PTs • Completed suicide • Suicidal ideation • Suicide attempt • Depression suicidal

	• Suicidal behavior
Any type of conjunctivitis or blepharitis (severe or serious)	broad CMQ conjunctivitis (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) Blepharitis PTs (Blepharitis, blepharitis allergic) **AND** Serious AE= "Yes" OR Severity= "severe" Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Keratitis	Any of the following PTs: a. Keratitis b. Allergic keratitis c. Ulcerative keratitis d. Atopic keratoconjunctivitis e. Herpes ophthalmic f. − Ophthalmic herpes simplex Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.

[1] 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

10.5. Algorithm for RESCUE TREATMENTS

1. **Not required to adjudicate rescue treatment:**

   Post-baseline medications (WHODD-coded) given for indications consistent with AD[1].

   a. Always considered rescue:
      - ATC2 = CORTICOSTEROIDS FOR SYSTEMIC USE
      - ATC2 = IMMUNOSUPPRESSANTS
      - 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
      - Preferred Drug Name = Crisaborole, if used after day 29
      - ATC2 = CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, if used after day 29
      - Preferred Drug Name = Tacrolimus, if used after day 29
      - Preferred Drug Name = Pimecrolimus, if used day 29

   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

[1] 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. **Require 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

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