REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

NCT03345914

Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical corticosteroids in patients, ≥ 6 years to <12 years of age, with severe Atopic Dermatitis

Protocol: R668-AD-1652.03

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

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List of abbreviations and definition of terms

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BAS	Biomarker analysis set
BSA	Body surface area
BUN	Blood urea nitrogen
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
DFI	Dermatitis Family Index
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
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
NAb	Neutralizing antibody
PCSV	Potentially clinically significant value
PD	Pharmacodynamics

PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term
QW	Weekly
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SE	Standard error
SOC	System organ class
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of the study data. This SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for the R668-AD-1652 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 one of the most common skin disorders in infants and children. The disease affects over 20% of children in many industrialized countries. A total of 45% of all cases of AD begin within the first 6 months of life, 60% begin during the first year, and 85% begin before 5 years of age. Phase 3 of the International Study of Asthma and Allergies in Childhood (ISAAC) showed a 1-year period prevalence rate for AD in the 6 to 7 year age group to be 15% or more in Australia, England, and Scandinavia. A study conducted in the United States (US) in school-going children aged 5 to 9 years old showed similar prevalence rate of around 17%.

There is currently a high unmet medical need for a safe and effective therapy for AD in young 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 a supportive role, especially in children with moderate-to-severe disease. Pharmacological management of AD in children is mainly limited to topical therapy with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). However, long-term use of TCS in children is not recommended because of the risk of irreversible skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, growth retardation, hypothalamic pituitary axis effects, etc). Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are also used in AD as an alternative to or in combination with TCS. The more effective TCI products (tacrolimus 0.1%) are not approved for use in children aged 6 to 11 years old. Moreover, the use of TCI is frequently associated with skin irritation. Furthermore, a possible increased risk of malignancy (lymphoma and skin cancers) has been noted for TCIs (refer to products' US prescribing information).

Systemic agents are used off-label in children aged 6 to 11 years old (cyclosporine, systemic steroids, methotrexate, azathioprine, and mycophenolate mofetil). A recent survey conducted in Europe, "European Treatment of Severe Atopic Eczema in Children Taskforce (TREAT)" found that approximately 70% of respondents initiated systemic therapy for children with severe AD. All of these systemic agents have significant side effects in children, including stunted growth,

diabetes, cutaneous atrophy, hypertension, osteoporosis, and rebound exacerbation after discontinuation (corticosteroids), myelosuppression and hepatotoxicity (methotrexate), nephrotoxicity and hypertension (cyclosporine), increased risk of malignancies (cyclosporine, azathioprine), 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.

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

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab administered concomitantly with TCS in patients, ≥6 years to <12 years of age, with severe AD.

1.2.2. Secondary Objectives

The secondary objective of the study is to assess the safety of dupilumab administered concomitantly with TCS in patients ≥6 years to <12 years of age with severe AD.

1.2.3. Modifications from the Statistical Section in the Final Protocol

None.

2. INVESTIGATIONAL PLAN

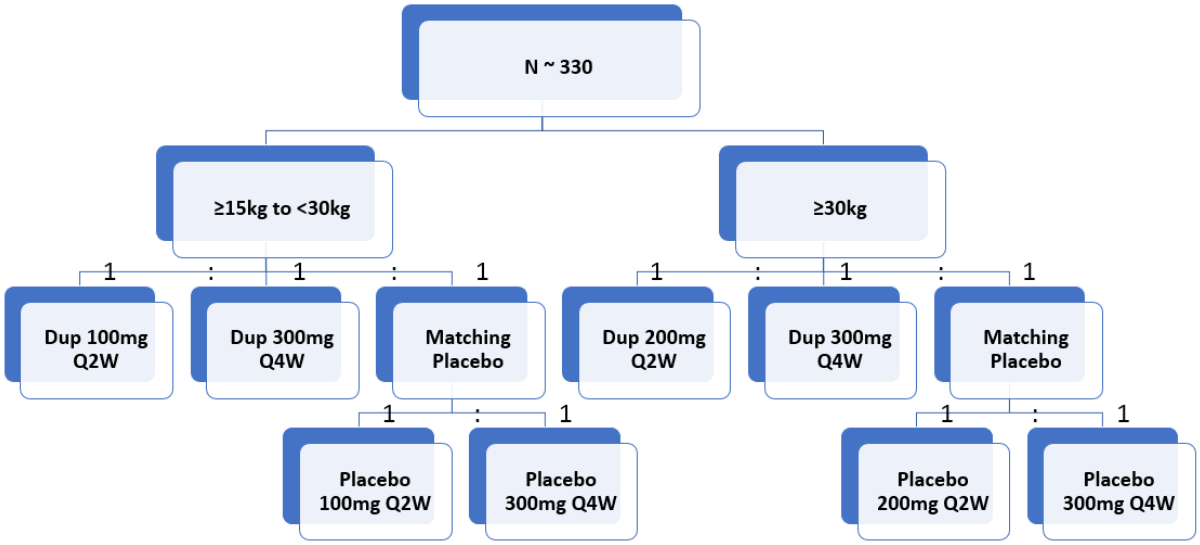
2.1. Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, parallel-group study in which study treatments (dupilumab/placebo) will be administered concomitantly with TCS. The study population will include patients ≥6 years to <12 years of age with severe AD whose disease cannot be adequately controlled with topical medications. Approximately 330 study patients are planned to be enrolled in the study.

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 body weight (<30 kg and ≥30 kg) (Figure 1) and region (North America, Europe) as follows:

- dupilumab Q2W treatment group combined with TCS (dupilumab Q2W + TCS):
  - Patients with baseline weight <30 kg will receive Q2W SC injections of 100 mg dupilumab (0.7 mL of a 150 mg/mL solution) from week 2 to week 14, following a loading dose of 200 mg on day 1.
  - Patients with baseline weight ≥30 kg will receive Q2W SC injections of 200 mg dupilumab (1.14 mL of a 175 mg/mL solution) from week 2 to week 14, following a loading dose of 400 mg on day 1
- dupilumab Q4W treatment group combined with TCS (dupilumab Q4W + TCS): all patients regardless of weight will receive Q4W SC injections of 300 mg dupilumab (2 mL of a 150 mg/mL solution) from week 4 to week 12, following a loading dose of 600 mg on day 1.
- placebo treatment group combined with TCS (Placebo + TCS): Patients will receive matching placebo (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding, the patients in the <30 kg weight stratum will be randomly assigned to receive, in a 1:1 ratio, either Q2W SC injections of placebo (0.7 mL) matching the 100 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or Q4W SC injections of placebo (2 mL) matching the 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥30 kg weight stratum, the patients randomized to the placebo group will receive, in a 1:1 ratio, either Q2W SC injections of placebo (1.14 mL) matching the 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or Q4W SC injections of placebo (2 mL) matching the 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

Figure 1: Randomization Scheme



Arm A consists of patients receiving Q2W treatment, either 100 mg for patients weighing <30 kg or 200 mg for patients weighing ≥30 kg. Arm B consists of patients receiving Q4W treatment , 300 mg regardless of weight. Arm C consists of patients receiving placebo treatment Q2W and Q4W and matching the dupilumab Q2W and Q4W dose regimens.

2.2. Sample Size and Power Considerations

Due to an inadvertent operational error, 68 patients were potentially unblinded. Details about the error and why it may have been unblinding will be described in the clinical study report. An additional approximately 90 patients were added to the study to ensure that the original number of blinded patients for all treatment groups is available for sensitivity analyses that exclude the potentially unblinded patients. This will maintain study balance and power.

Initially it is estimated that with 80 patients per group, at the 2-sided 5% significance level, the study will have a power table shown as below:

	Placebo + TCS (N=80)	Dupilumab 100mg/200mg Q2W + TCS (N=80)			Dupilumab 300mg Q4W + TCS (N=80)		
		Q2W + TCS	Treatment Difference	Power	Q4W + TCS	Treatment Difference	Power
Proportion of patients with IGA score 0 or 1 at week 16 (%)	5%	28%	23%	97%	22%	17%	87%
Proportion of patients with EASI-75 at week 16 (%)	17%	68%	51%	99%	62%	45%	99%

The significance level is set to 2-sided, 0.05 level. At the time the study was designed, there were no data available on the effects of dupilumab in pediatric patients. The assumptions used for the power calculations were estimated based on results from the R668-AD-1224 study (phase 3 combination study with TCS for adult AD patients) and R668-AD-1021 study (a phase 2b dose-ranging study in adults with AD) for patients with IGA=4 at baseline. Based on the result from the R668-AD-1021 study, the efficacy profile for dupilumab 200 mg Q2W was similar to dupilumab 300 mg Q2W. Therefore, the adult efficacy results from dupilumab 300 mg Q2W were used to assume the treatment effect for dupilumab 100mg/200mg Q2W in the study. This was a conservative assumption as it was expected that the effect of dupilumab in children would be greater than that seen in adults. The sample size calculations were done using nQuery (Version 7.0).

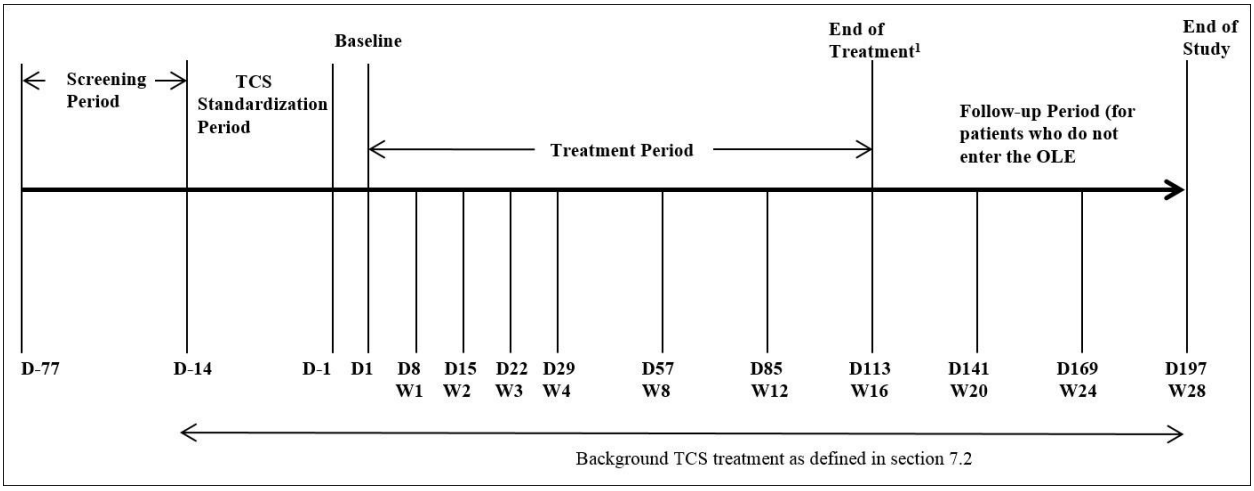
Adding 90 patients, the total sample size of the study will be up to approximately 330 patients (110 patients per group), or approximately 262 patients (80, 91 and 91 in Q2W, Q4W, and placebo group, respectively) if the potentially unblinded patients are excluded. With the sample size of 330 patients or 262 patients, the power for the co-primary endpoints will be greater than 90%.

2.3. Study Plan

The study will consist of the following periods (Figure 2):

1. Screening of up to 9 weeks,
2. TCS standardization period of 2 weeks,
3. Treatment period of 16 weeks, and
4. Follow-up of 12 weeks (for patients who do not enter the OLE)

Figure 2: Study Flow Diagram



D = study day; W = study week
Note: The length of the screening period is not fixed, but the screening period and TCS standardization must not exceed 77 days. The length of the TCS standardization period is fixed at 14 days.
1 For patients who enter the OLE, week 16 is the end of study.

After the parents or legal guardians provide informed consent and patients provide assent, the patients will be assessed for study eligibility at the screening visit. During the screening period, systemic treatments for AD will be washed out, as applicable, according to the eligibility requirements. The use of TCS (±TCI) will be permitted at the discretion of the investigator during the screening period until day -14. Starting on day -14, all patients will initiate a standardized TCS treatment regimen according to the guidelines. Patients may be rescreened, 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.

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 body weight (<30 kg and ≥30 kg) (Figure 1) and region (North America, Europe).

During the treatment period, patients will have weekly in-clinic visits through week 4, and then in-clinic visits Q4W through week 16 with weekly telephone visits in between the in-clinic visits. Parents/caregivers will be trained on injecting study drug during in-clinic visit 3 (day 1), visit 5 (week 2), and visit 7 (week 4) (this only applies to patients who will receive Q2W treatment during the study). During weeks in which no in-clinic visit is scheduled, the parent/caregiver will administer study drug to the patient. In case the parent/caregiver does not want to administer study drug to patient, they 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 Appendix 10.2. The end of treatment period visit will occur at week 16, two weeks after the last dose of study drug for patients randomized to the Q2W treatment group or placebo Q2W group, and 4 weeks after the last dose of study drug for patients randomized to the Q4W treatment or placebo Q4W group. 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 OLE study. All patients will be offered the opportunity to screen for entry into the OLE study at the end of the treatment period (week 16).

Patients who decline to enroll in the OLE study or those who fail eligibility criteria for the OLE study will have a 12-week follow-up period. For these patients, after week 16, follow-up visits will occur every 4 weeks from week 20 to week 28. During the follow-up period, patients will be monitored for safety and tolerability and have laboratory and clinical assessments as noted in Appendix 10.2.

3. ANALYSIS POPULATIONS

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

3.1. The 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). All efficacy variables will be evaluated in the FAS, which will be considered to be the primary analysis set.

The modified full analysis set (mFAS) includes all randomized patients but excludes potentially unblinded patients. The primary endpoint, co-primary endpoint, and selected secondary endpoints will be evaluated in the mFAS as sensitivity analyses.

The per protocol set (PPS) includes all patients in the FAS except for those who are excluded because of major protocol violations. A preliminary list of potential major protocol violations is provided in Appendix 10.3 and a final list will be generated prior to database lock. The PPS will also exclude potentially unblinded patients.

The primary and co-primary endpoints will also be evaluated in the PPS.

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 "as treated" assignments will be made as follows:

Randomized to	Treatment Received	Treatment Assignment
Dupilumab (any regimen)	All placebo	Placebo
Dupilumab (any regimen)	≥ 1 Dupilumab (any regimen)	Original randomization group
Placebo	1 Dupilumab (any regimen)	Dupilumab regimen received
Placebo	> 1 Dupilumab (any regimen)	First Dupilumab regimen received [1]

[1] For example, a patient was randomized to Placebo group but received one 100mg Dupilumab and one 200mg Dupilumab accidently. This patient will be assigned to 100mg Q2W Dupilumab treatment group.

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 the 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.

3.4. The Immunogenicity Analysis Set (AAS)

The ADA population 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 NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least one non-missing result in the NAb assay [patients who are ADA negative are set to negative in the NAb analysis set].

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 (≥6 to <9, ≥9 to <12), sex, ethnicity, race, baseline weight (kg) with grouping (<30 kg, >=30 kg), height (m), BMI (kg/m^2) with grouping (<20, >=20)
- Baseline characteristics: Duration of AD disease with grouping (< 5 years, >=5 years), worst itch score, 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 impression of disease, Patient Oriented Eczema Measure (POEM), Children's Dermatology Life Quality Index (CDLQI), Global Individual Signs score (GISS), Dermatitis Family Index (DFI) and Patient Reported Outcomes Measurements Information Systems (PROMIS) anxiety and depression score

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, azathioprine and other treatments) during the last 6 months will also be collected.

4.3. Prior / Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded 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.

Prior 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 nonsteroidal immunosuppressant (may be used as rescue)
- Treatment with systemic corticosteroids (may be used as rescue)
- Treatment with crisabarole
- Treatment with TCI

Note: The use of TCI is prohibited during the 2-week standardization period leading up to the baseline visit, and the treatment and follow-up periods

- Treatment with high-potency or very high potency TCS, (high potency TCS 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. Investigators will be required to perform an IGA assessment prior to starting rescue treatment and initiate rescue treatment only in patients who either have an IGA score = 4 or have intolerable symptoms. If possible, investigators are encouraged to consider rescue initially with topical treatment (e.g., high potency TCS) and to escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. Patients may continue study treatment if rescue consists of topical medications.

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

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 EMA and EMA Reference Market Countries only, the co-primary endpoints are:

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

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument to rate AD disease severity globally in clinical studies. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration. IGA score will be assessed at the scheduled and unscheduled clinic visits according to Appendix 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 of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights. For patients of age >=8 years, the weights are 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. For patients of age <8 years, the weights are 20% = head, 20% = upper extremities, 30% = trunk, 30% = 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 worst itch score

Worst itch scale

The worst itch scale is a simple assessment tool that patients will use to report the intensity of their pruritus (itch). This tool is composed of two questions and each question is an 11-point scale (0 to 10) in which 0 indicates no itching while 10 indicates worst itching possible. Patients will be asked the following 2 questions:

- "What was the worst itch you had today?"
- "What was the worst itch you had last night?"

Patients will be asked to provide answers to these 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period; see time point in Appendix 10.2). The daily worst itch score will be calculated as the worse of the scores for the 2 questions on a given day. Any day with one score only should be discarded as a "missing score day".

Patients will be instructed on using the patient diary to record their worst itch score at the screening and baseline visits. Clinical sites will check and remind patients to complete the diary at each visit.

The baseline worst itch scale score is defined as the prorated average of the worst itch scale scores reported continuously for 7 days right before the baseline visit (i.e. study day -7 to day -1). A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For post-baseline worst itch scale score, the weekly mean of daily worst itch score is calculated as the prorated average of the reported daily worst itch score within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3.

Other secondary endpoints are:

- Change from baseline to week 16 in weekly average of daily worst itch score
- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Change from baseline to week 16 in percent BSA affected by AD
- Percent change from baseline to week 16 in SCORAD
- Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline at week 16
- Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline to week 16
- Time to onset of effect on pruritus during the 16-week treatment period (≥4 point reduction of weekly average of daily worst itch score from baseline)
- Time to onset of effect on pruritus during the 16-week treatment period (≥3 point reduction of weekly average of daily worst itch score from baseline)
- Change from baseline to week 16 in CDLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in Dermatitis Family Index (DFI)
- Change from baseline to week 16 in Patient Reported Outcomes Measurements Information Systems (PROMIS) pediatric anxiety short form scale score
- Change from baseline to week 16 in PROMIS pediatric depressive symptoms short form scale score
- Topical treatment for AD – proportion of TCS medication-free days from baseline to week 16
- Mean weekly dose of TCS in grams for low or medium potency TCS from baseline to week 16
- Mean weekly dose of TCS in grams for high potency TCS from baseline to week 16
- Incidence of skin-infection TEAEs (excluding herpetic infections) through week 16*
- Incidence of serious TEAEs through week 16

*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 and will be reported as a percentage of all major body sections combined. The possible highest score for each region is:

	Head	Torso	Lower Extremities	Upper Extremities	Genitals
Age 10 and older	9%	36%	36%	18%	1%
Age 9	10%	36%	36%	18%	0%
Age 8	11%	36%	35%	18%	0%
Age 7	12%	36%	34%	18%	0%
Age 6	13%	36%	33%	18%	0%

Total BSA will be the sum of all individual body areas. Patients will undergo this assessment at the scheduled and unscheduled clinic visits according to Appendix 10.2 _Schedule_of_Events.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). The extent of AD is assessed by the Investigator as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms (erythema, oedema / papulation, excoriations, lichenification, oozing / crusts and dryness) of AD is assessed by the Investigator using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as A/5 + 7B/2 + C. The maximum SCORAD score is 103. The objective SCORAD is calculated as A/5 + 7B/2. The maximum objective SCORAD score is 83.

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

Handling missing items from CDLQI:

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
ii. If two or more questions are left unanswered the questionnaire is not scored.
iii. If two or more response options are ticked for one question, the response option with the highest score should be recorded.
iv. The CDLQI 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.

This questionnaire asks the caregiver to report their perception of patient's AD symptoms. It is therefore completed by the caregiver.

Dermatitis Family Index (DFI)

The impact on family life has been documented in families of children with very severe AD. The DFI was the first instrument assessing the impact of having a child with AD on family QOL (Lawson 1998). The 10-item disease specific questionnaire was formed after ethnographical interviews and focus groups revealed the areas of family QOL affected by AD. The self-administered instrument is completed by an adult family member of a child affected by dermatitis. The items inquire about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships and the impact of helping with treatment on the primary caregiver's life. The DFI questions are scored on a four-point Likert scale ranging from 0 to 3, so that the total DFI score, which is calculated as sum of all 10 questions, ranges from 0 to 30. The time frame of reference is the past week. A higher DFI score indicates greater impairment in family QOL as affected by AD. The DFI will be assessed at time points according to Appendix 10.2.

Handling missing items from DFI:

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
ii. If two or more questions are left unanswered the questionnaire is not scored.
iii. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

PROMIS Anxiety and Depression Scales

The PROMIS Anxiety instrument measures self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). The PROMIS Depression instrument assesses self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). This questionnaire asks the caregiver to report their perception of the patient's anxiety and depressive symptoms. It is therefore completed by the caregiver.

Each question has five response options ranging in value from 1 to 5 (1= Never, 2= Almost never, 3=Sometimes, 4= Often, 5= Almost Always). For an 8-item form, the lowest possible total raw score is 8; the highest possible total raw score is 40. For a 6-item form, the lowest possible total raw score is 6; the highest possible total raw score is 30. The scoring algorithm is as follows.

1. Calculate the total raw score as the sum of values of response to each question answered.
2. If some questions are not answered, calculate the pro-rated raw score as

$$\frac{\text{raw sum*number of items on the form}}{\text{number of items that were actually answered}}$$

1. Locate the applicable score conversion table in Appendix 10.7 and use this table to translate the total raw score or pro-rated score into a T-score for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore a person with a T-score of 40 is one SD below the mean. The standardized T-score is reported as the final score for each participant.

The PROMIS will be assessed 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 impression of disease: proportion of patients with not itchy at all and proportion of patients with not itchy at all or a little itchy at week 16
- Patient global impression of change: proportion of patients who rate their eczema symptoms as "much better" at week 16
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Number of missed school days during the treatment period
- Number of caregiver missed workdays during the treatment period
- Mean VAS score of injection site pain as assessed by Faces pain scale for all visits through week 16
- Change from baseline to week 16 in sleep quality evaluation
- Proportion of patients with IGA score 0 or 1 or EASI-90 at week 16

Patient Global Impression of Disease

Patients will rate their disease based on a 5-point Likert scale. Patients will be asked: "In general, how itchy have you been during the last 7 days?". Response choices are: "Not itchy at all" (1); "A little itchy" (2); "Medium itchy" (3); "Pretty itchy" (4); "Very itchy" (5). Patients will undergo this assessment at time points according to Appendix 10.2.

Patient Global Impression of Change

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale. Patients will be asked: "Since you started your study medication, how has your itching changed?" Response choices are: "Much better" (1); "A little better" (2); "No difference" (3); "A little worse" (4); "Much worse" (5). Patients will undergo this assessment at time points according to Appendix 10.2.

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.

Faces pain scale - Revised

The Faces Pain Scale – Revised (FPS-R) is a self-report measure of pain intensity developed for children. It was adapted from the Faces Pain Scale to make it possible to score the sensation of pain on the widely accepted 0 to 10 metric. The possible pain scale are 0, 2, 4, 6, 8 and 10. The

instrument will be used to assess injection site pain at the time points specified at visits according to Appendix 10.2.

Assessment of Missed School Days

Patients who are enrolled in school will be asked to report the number of missed school days since the last study assessment. Patients will undergo this assessment at time points according to Appendix 10.2. This questionnaire is completed by the caregiver.

Caregiver Assessment of Missed Workdays

Caregivers who are employed will be asked to report the number of sick-leave days since the last study assessment. Caregivers will undergo this assessment at the time points according to Appendix 10.2.

Sleep Disturbance

Sleep disturbance will be evaluated using 3 scores as listed below:

- Assessment of sleeplessness from SCORAD (score ranged from 0 to 10)
- Question 9 "Over the last week, how much has your sleep been affected by your skin problem?" from CDLQI (score ranged from 0 to 3)
- Question 2 "Over the last week, on how many nights has your sleep been disturbed because of the eczema?" from POEM (score ranged from 0 to 4)

SCORAD, CDLQI and POEM will be assessed at time points according to Appendix 10.2.

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 and follow-up 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)/TEAE category

- Systemic or extensive hypersensitivity reactions, including anaphylactic reactions
- Malignancy
- Helminthic infections
- Suicide-related events
- Conjunctivitis (any type or etiology), keratitis or blepharitis (only events that are either severe or serious will be reported as AESIs)

Appendix 10.5 provides a list of AESIs search criteria.

Other adverse events:

- Narrow conjunctivitis is defined as the following PT terms
  - Conjunctivitis
  - Conjunctivitis allergic
  - Conjunctivitis bacterial
  - Conjunctivitis viral
  - Atopic Keratoconjunctivitis
- Broad conjunctivitis is defined as the following PT terms
  - Conjunctivitis, Conjunctivitis allergic
  - Conjunctivitis bacterial
  - Conjunctivitis viral
  - Atopic Keratoconjunctivitis
  - Blepharitis
  - Dry eye
  - Eye irritation
  - Eye pruritus
  - Lacrimation increased
  - Eye discharge
  - Foreign body sensation in eyes
  - Photophobia, Xerophthalmia
  - Ocular hyperaemia
  - Conjunctival hyperaemia
- Keratitis is defined as the following PT terms
  - Keratitis
  - Allergic keratitis
  - Ulcerative keratitis
  - Corneal infection
  - Atopic keratoconjunctivitis
  - Herpes ophthalmic
- Eczema Herpeticum is defined as the following PT terms
  - Eczema herpeticum

- Herpes Zoster is defined as the following PT terms
  - Herpes zoster
  - Ophthalmic herpes zoster
- Muco-cutaneous herpes simplex infections is defined as the following PT terms
  - Oral herpes
  - Genital herpes
  - Herpes simplex
  - Herpes virus infection
  - Nasal herpes

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).

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 for patients receiving Q2W treatment and day 1, week 4, and week 8 for patients receiving Q4W treatment), sitting blood pressure, heart rate, and respiratory rate will also be assessed at 30 (±10) minutes postdose and then at 2 hours (±15 minutes). 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).

4.5.6. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] =QT/[$RR^{0.33}$] and QTc Bazett [QTcB]=QT/[$RR^{0.5}$]) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. See Appendix 10.2 for assessment time points.

4.6. Pharmacokinetic (PK) Variables

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Appendix 10.2 . PK parameters may include, but are not limited to C_{trough} and $C_{trough,SS}$.

4.7. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status and time-point/visit. Serum samples for anti-dupilumab antibody will be collected at time points according to visit schedule (Appendix 10.2). ADA analysis will be conducted on samples collected at baseline, EOT and EOS. ADA sample at Week 4 will only be analyzed for ADA in patients positive for ADA in a later visit such as EOT or EOS.

4.8. Biomarkers Variables

Biomarkers to be analyzed in this study are:

- TARC
- Total serum IgE
- Immunoglubin profiling
- 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, median, standard deviation, first quartile (Q1), third quartile (Q3), minimum, and maximum.

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

All data will be summarized by 3 treatment groups (i.e. dupilumab q2w dose, dupilumab q4w dose and 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 (high potency 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 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 potentially unblinded

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
- A listing of patients potentially unblinded

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:

Q2W dosing: (Date of last study drug injection – date of first study drug injection) + 14 days

Q4W dosing: (Date of last study drug injection – date of first study drug injection) + 28 days

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, Q1, medians, Q3 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 (≥6 to <9, ≥9 to <12)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black or African American, Asian, Other)
- Duration of AD (< 5 years, ≥5 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 (<30 kg, ≥30 kg)
- BMI (<20, ⩾20)
- Region (North America, Europe)
- Baseline severe EASI (<25, ≥25)
- Baseline moderate-to-severe EASI (<20, >=20)
- Baseline worst itch scale (<7, ≥7)
- Body Surface Area (BSA) (≥10%-<30%, ≥30%-<50%, ≥50%)
- Baseline SCORAD score ((<50, ≥50)
- Previous usage of ciclosporin (CsA) (Yes, No)
- Previous usage of methotrexate (MTX) (Yes, No)
- Previous usage of Azathioprine (Aza) (Yes, No)
- Previous use of systemic immunosuppressants for AD (Yes, No)
- History of asthma (Yes, No)
- History of nasal polys (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 (baseline weight group (<30 kg or ≥30kg) and region (North America or Europe) 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. 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.

All efficacy data, regardless of whether the patient remains on 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 of whether 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.

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 the FAS, which will be considered as the primary analysis. Evaluation of primary and co-primary endpoints in the mFAS and PPS will be considered as sensitivity analyses.

5.7.2. Analyses of Secondary Efficacy Variables

All secondary endpoints will be evaluated on the FAS. Selected secondary endpoints will be evaluated in the mFAS as sensitivity analyses.

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

The continuous endpoints will be analyzed using analysis of covariance (ANCOVA) model as the primary analysis method with multiple imputation (MI) method for missing data. Patients' efficacy data through week 16 after the rescue treatment use will be set to missing first, and then be imputed by MI method. To account for the uncertainty in the imputation, missing data from the FAS will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates including treatment groups, randomization strata (baseline weight group and region), and relevant baseline.

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

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, the baseline value and the randomization strata (baseline weight group and region)
- 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 worst itch scale 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 Pruritus worst itch scale >=4 and >=3 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 either event during the treatment period will have their time censored at the end of treatment period. These times 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.

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

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-1 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	Dupilumab q2w group
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	7	1
Co-primary endpoint for EMA and EMA Reference Market Countries only, key secondary for US	Proportion of patients with EASI-75 (>=75% improvement from baseline) at week 16	8	2
Secondary endpoints	Percent change in EASI score from baseline to week 16	9	3
	Proportion of patients with EASI-50 at week 16	10	4
	Percent change from baseline to week 16 in weekly average of daily worst itch score	11	5
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline at week 16	12	6
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline at week 16	15	13
	Proportion of patients with EASI-90 at week 16	16	14
	Change from baseline to week 16 in POEM	20	17
	Change from baseline to week 16 in CDLQI	21	18
	Percent change from baseline to week 16 in SCORAD	22	19

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, treatment by randomization strata interaction and treatment by subgroup interaction as factors. P-values for the interaction term will be reported. We will consider interaction effect as significant if P-value is greater than 0.1.

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 10.4. 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 (≥6 to <9, ≥9 to <12)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black, Asian, Other)
- Duration of AD (< 5 years, ≥5 years)
- Baseline BMI (<20, ≥20)
- Baseline weight group (<30 kg, ≥30 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 10.4) 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 concentrations in serum at each sampling time by dose
- Graphical presentations of median and mean (+/- SD) functional dupilumab concentration in serum vs nominal time profiles
- Graphical presentations of individual functional dupilumab concentration in serum vs actual sampling time profiles
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum.

No formal statistical analysis will be performed.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.7 will be summarized using descriptive statistics in the ADA analysis set. Frequency tables of the proportion of patients with pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent ADA responses, and titer categories will be presented as absolute occurrence (n) and percent of patients (%) by treatment groups.

ADA response categories and titer categories are defined as follows:

- 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
- Treatment-emergent response, 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, 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.
- 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
- Maximum Titer Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

The following summaries will be provided based on AAS:

- Number (%) of ADA-negative patients
- Number (%) of patients with pre-existing immunoreactivity by treatment group and ADA titer categories
- Number (%) of treatment-emergent ADA-positive patients by treatment group and ADA titer categories
  - Number (%) of persistent treatment-emergent ADA-positive patients

  - Number (%) of indeterminate treatment-emergent ADA-positive patients
  - Number (%) of transient treatment-emergent ADA-positive patients
  - Number (%) of treatment-boosted ADA-positive patients
- Listing of all ADA peak titer levels will be provided for treatment emergent and treatment boosted ADA response subjects and the neutralizing antibody status will be provided for subjects positive in the ADA assay.
- Scatter plot of ADA titers by ADA assessment time point indicated in Appendix 10.2
- Number (%) of patients in the three ADA titer categories by treatment group

5.10.2. Analysis of Neutralizing Antibodies (NAb)

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

5.11. Association of Immunogenicity with Exposure, Safety and Efficacy

5.11.1. Immunogenicity and Exposure

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

5.11.2. Immunogenicity on Safety and Efficacy

Association between ADA response categories and safety events will focus on the following events:

- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Number (%) of patients with the above mentioned safety events will be summarized by treatment-emergent, treatment-boosted, persistent ADA response status, and neutralizing antibody status during the TEAE period.

Association between ADA and the primary and key secondary efficacy endpoints may be explored and summarized in SAF using individual patient spaghetti plots.

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

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points
- Patients with persistent ADA response

- NAb positive patients, that is patients who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer level in treatment-emergent or treatment-boosted ADA positive patients:
  - 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)
- Lactate dehydrogenase (LDH)

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

Exploratory analyses for the difference between dupilumab groups and placebo on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group as a fixed effect, and the relevant baseline values as covariate. Missing 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) with the following clinical endpoints will be explored using ANCOVA model. The model includes the below clinical endpoint as the dependent variable and the log10 based transformed baseline biomarker data, treatment group and their interaction as the predictor variables. Model coefficients and P-value will be provided to indicate significance of the correlation/association.

- Percent change from baseline to week 16 in EASI score
- Percent change from baseline to week 16 in weekly average of worst itch scale
- 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 logistic model. The model includes the responder/nonresponder of below clinical endpoint as the dependent variable and the log10 based transformed baseline biomarker data, treatment group and their interaction as the predictor variables. Model coefficients and P-value will be provided to indicate significance of the correlation/association.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of worst itch scale ≥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 weight. The risk ratio and p-value will be provided.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of worst itch scale ≥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.

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

For the biomarkers with at least 5 evaluable patients in both the dupilumab and placebo treatment groups at Week 16, a Cochran-Mantel-Haenszel test will be conducted to compare the proportion of patients achieving normalized status across treatment groups, stratified by randomization strata (baseline weight group and region), for both the main (LOCF) and sensitivity (OC) analysis approaches. The test statistic p-values for the comparison of the dupilumab groups versus placebo and point estimate with 95% confidence interval will be provided. The proportions will be also summarized by treatment group at each assessment visit.

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

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

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

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

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

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

6.2. General Data Handling Conventions

For the laboratory safety variables data, if the data 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, ECG, ADA) will be summarized by the study scheduled visits described in the study protocol and SAP "Schedule of Events". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination (ET) visit 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 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 diary study day -7 to -1 = BL, 1 to 7 = week 1, 8 to 14 = week 2, etc, with 7 days interval between visit windows.

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 worst itch score	• % change from baseline • reduction of ≥4 points from baseline • reduction of ≥3 points from baseline • Change from baseline • Time to event	• CMH test adjusted by randomization strata for categorical variables • multiple imputation (MI) with ANCOVA for continuous variables • Cox model for time to event endpoint.	Yes for % change and reduction >=4	Yes for % change and reduction >=4
Body Surface Area (BSA) Involvement of Atopic Dermatitis	• % change from baseline • Change from baseline	• multiple imputation (MI) with ANCOVA	No	No
Parameter(s)	**Endpoints**	**Primary Statistical Method**	**Supportive/Sensitive Statistical Method**	**Subgroup Analysis**
SCORing Atopic Dermatitis (SCORAD)	• % change from baseline • Change from baseline • SCORAD50	• multiple imputation (MI) with ANCOVA for continuous variables • CMH test adjusted by randomization strata	No	No

	• SCORAD75 • SCORAD90	for categorical variables		
Dermatitis Family Index(DFI)	• % change from baseline Change from baseline	• multiple imputation (MI) with ANCOVA	No	No
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 • reduction of ≥3 points from baseline • reduction of ≥4 points from baseline	• multiple imputation (MI) with ANCOVA for continuous variables • CMH test adjusted by randomization strata for categorical variables	No	No
Children Dermatology Life Quality Index (CDLQI)	• Change from baseline	• multiple imputation (MI) with ANCOVA for continuous variables	No	No
PROMIS anxiety and depression score	• % change from baseline • Change from baseline •	• 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/Sensitive Statistical Method**	**Subgroup Analysis**
Patient Global Impression of disease	• Number (%) of patients with not itchy at all • Number (%) of patients with not itchy at all or a little itchy	• CMH test adjusted by randomization strata	No	No
Patient Global Impression of Change	• 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 days	• Descriptive statistics by visit/time	No	No
Assess caregiver missed workdays	• Number of days	• Descriptive statistics by visit/time	No	No

Faces Pain Scale	• Mean VAS score of injection site pain	• Descriptive statistics by visit/time	No	No
TCS	• Proportion of TCS medication-free days from baseline to week 16 • Mean weekly dose of TCS in grams for low or medium potency TCS from baseline to week 16 • Mean weekly dose of TCS in grams for high potency TCS from baseline to week 16	• CMH test adjusted randomization strata • ANCOVA for continuous variables	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, TCS Standardization, Baseline, and Treatment Period)

	Screening		Treatment Period																
		TCS standardization	BL																EOT[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V 6	V7	PV 8[1]	PV 9[1]	PV 10[1]	V 11	PV 12[1]	PV 13[1]	PV 14[1]	V 15	PV 16[1]	PV 17[1]	PV 18[1]	V 19
Week (W)				W1	W2	W 3	W4	W5	W6	W7	W8	W9	W10	W11	W 12	W 13	W 14	W 15	W 16
Study Day (D)	D -77 to D -14	D -14 to D-1	D1	D8	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64	D 71	D 78	D 85	D 92	D 99	D 106	D 113
Window in days				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Screening/Baseline:																			
Informed consent/assent	X																		
[redacted]	X																		
Medical history	X																		
Ophthalmology exam	X																		
Demographics	X																		
Inclusion/exclusion criteria	X		X																
Randomization			X																
Patient and/or parents/caregiver diary training[3]	X	X	X																
Treatment:																			
Injection training/observation (patients receiving Q2W			X		X		X												

	Screening		**Treatment Period**																
		TCS standardization	**BL**																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V 6	V7	PV 8[1]	PV 9[1]	PV 10[1]	V 11	PV 12[1]	PV 13[1]	PV 14[1]	V 15	PV 16[1]	PV 17[1]	PV 18[1]	V 19
Week (W)				W1	W2	W 3	W4	W5	W6	W7	W8	W9	W10	W11	W 12	W 13	W 14	W 15	W 16
Study Day (D)	D -77 to D -14	D -14 to D-1	D1	D8	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64	D 71	D 78	D 85	D 92	D 99	D 106	D 113
Window in days				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
treatment)[4]																			
Study drug administration (patients receiving Q2W treatment)			X[5]		X[5]		X[5]		X		X		X		X		X		
Injection observation (patients receiving Q4W treatment)[5]			X				X				X								
Study drug administration (patients receiving Q4W treatment)			X[5]				X[5]				X[5]				X				
Patient and/or parents/caregiver diary completion to record self-admin of study drug (patients receiving Q2W treatment)									X				X				X		
Study drug dispensing (patients receiving Q2W treatment) [6]							X				X				X				
Study drug accountability (patients											X				X				X

	Screening		Treatment Period																
		TCS standardization	**BL**																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V 6	V7	PV 8[1]	PV 9[1]	PV 10[1]	V 11	PV 12[1]	PV 13[1]	PV 14[1]	V 15	PV 16[1]	PV 17[1]	PV 18[1]	V 19
Week (W)				W1	W2	W 3	W4	W5	W6	W7	W8	W9	W10	W11	W 12	W 13	W 14	W 15	W 16
Study Day (D)	D -77 to D -14	D -14 to D-1	D1	D8	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64	D 71	D 78	D 85	D 92	D 99	D 106	D 113
Window in days				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
receiving Q2W treatment)																			
Review home diary		X	X	X	X	X	X				X				X				X
TCS application[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TCS dispensing		X	X	X	X	X	X				X				X				X
TCS accountability[8]			X	X	X	X	X				X				X				X
Patient and parents/caregiver counseling for diary completion		X	X	X	X	X	X				X				X				X
Patient recording of TCS use via diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient recording of emollient use via diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[9]																			
Patient assessment of pruritus intensity using worst itch score via diary (daily)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient global	X		X		X		X				X				X				X

	Screening		Treatment Period																
		TCS standardization	**BL**																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V 6	V7	PV 8[1]	PV 9[1]	PV 10[1]	V 11	PV 12[1]	PV 13[1]	PV 14[1]	V 15	PV 16[1]	PV 17[1]	PV 18[1]	V 19
Week (W)				W1	W2	W 3	W4	W5	W6	W7	W8	W9	W10	W11	W 12	W 13	W 14	W 15	W 16
Study Day (D)	D -77 to D -14	D -14 to D-1	D1	D8	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64	D 71	D 78	D 85	D 92	D 99	D 106	D 113
Window in days				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
impression of disease,[10,11]																			
Patient global impression of change[10,11]					X		X				X				X				X
CDLQI[10,11] POEM,[10,11] DFI[12], PROMIS anxiety and depression scale[10,11]	X		X		X		X				X				X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X	X	X	X				X				X				X
Faces pain scale for injection pain			X		X[13]		X				X				X				
Assess missed school days			X				X				X				X				X
Assess caregiver missed workdays			X				X				X				X				X
Photograph AD areas (select sites)			X																X
Safety:																			
Weight	X		X																X
Height	X		X																X

	Screening		Treatment Period																
		TCS standardization	**BL**																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V 6	V7	PV 8[1]	PV 9[1]	PV 10[1]	V 11	PV 12[1]	PV 13[1]	PV 14[1]	V 15	PV 16[1]	PV 17[1]	PV 18[1]	V 19
Week (W)				W1	W2	W 3	W4	W5	W6	W7	W8	W9	W10	W11	W 12	W 13	W 14	W 15	W 16
Study Day (D)	D -77 to D -14	D -14 to D-1	D1	D8	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64	D 71	D 78	D 85	D 92	D 99	D 106	D 113
Window in days				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Vital signs[5]	X	X	X	X	X	X	X				X				X				X
Physical examination	X																		X
ECG	X																		X
Adverse events[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing: [14]																			
Hematology	X		X				X				X								X
Chemistry	X		X				X				X								X
Urinalysis	X		X				X												X
Pregnancy test, WOCBP only	Ser		Ur		Ur[16]		Ur				Ur				Ur				
HIV, HBsAg, HBsAb, HBcAb, Hep C Ab, TB[15]	X																		
Biomarker:																			
TARC	X		X				X												X
Immunoglobulin profiling	X		X																X
[redacted]:																			
[redacted]			X																

	Screening		Treatment Period																
		TCS standardization	**BL**																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V 6	V7	PV 8[1]	PV 9[1]	PV 10[1]	V 11	PV 12[1]	PV 13[1]	PV 14[1]	V 15	PV 16[1]	PV 17[1]	PV 18[1]	V 19
Week (W)				W1	W2	W 3	W4	W5	W6	W7	W8	W9	W10	W11	W 12	W 13	W 14	W 15	W 16
Study Day (D)	D -77 to D -14	D -14 to D-1	D1	D8	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64	D 71	D 78	D 85	D 92	D 99	D 106	D 113
Window in days				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Drug Concentration and ADA:																			
Functional dupilumab concentration sample			X				X				X				X				X
ADA sample			X				X												X

BL = baseline; Ser = serum; Ur = urine; WOCBP = women of childbearing potential; TB = tuberculosis
Note: The length of the screening period is not fixed, but must not exceed 77 days. The length of the TCS standardization period is fixed at 14 days.

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

Study Procedure	**Follow-Up Period**[7]			**Unscheduled Visit**[8]	**Early Termination Visit**
			EOS		
In-clinic Visit (V)	V20	V21	V22		
Week (W)	W20	W24	W28		
Study Day (D)	D141	D169	D197		
Window in days	±4	±4	±4		
Treatment:					
Study drug accountability [1]				X	X
TCS application	X	X	X		
TCS dispensing	X	X		X	
TCS accountability	X	X	X	X	X
Patient recording of TCS use via diary	X	X	X	X	X
Patient recording of emollient use via diary	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X
Efficacy:[2]					
Patient assessment of pruritus intensity using worst itch score via diary (daily)	X	X	X	X	X
Patient global impression of disease	X	X	X	X	X
Patient global impression of change	X	X	X	X	X
Patient-reported CDLQI[3,4], POEM[3,4], DFI[5], PROMIS anxiety and depression scale[3,4]	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X	X
Assess missed school days	X	X	X	X	X
Assess caregiver missed work days	X	X	X	X	X
Photograph AD areas (select sites)			X		X
Safety					
Weight			X		X
Height			X		X
Vital signs	X	X	X	X	X
Physical examination			X	X	X
ECG			X	X	X
Adverse events[9]	X	X	X	X	X
Laboratory Testing:[6]					
Hematology			X	X	X

Study Procedure	**Follow-Up Period[7]**			**Unscheduled Visit[8]**	**Early Termination Visit**
			EOS		
In-clinic Visit (V)	V20	V21	V22		
Week (W)	W20	W24	W28		
Study Day (D)	D141	D169	D197		
Window in days	±4	±4	±4		
Chemistry			X	X	X
Urinalysis			X	X	X
Pregnancy test, WOCBP only			Urine	Urine	Urine
Biomarker:					
TARC			X	X	X
Immunoglobulin profiling			X	X	X
Drug Concentration and ADA Samples:					
Functional dupilumab concentration sample		X	X	X	X
ADA sample			X	X	X

EOS = End of Study

Footnotes for Schedule of Events Table 1

1. The site will contact the patient or parents/caregiver by telephone to conduct these visits. The parents/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.

[redacted].

3. Training of patients and parents/caregiver regarding completion of diary to record (a) administration of each dose of drug outside the clinic by parent/caregiver; (b) completion of the assessment of pruritus using worst itch scale; (c) emollient use; (d) TCS use
4. Parents/caregivers will be trained on how to administer study drug. This will enable administration at home in between clinic visits.
5. Patients will be monitored at the study site at visits 3, 5, and 7 (for patients receiving Q2W treatment) and at visits 3, 7, and 11 (for patients receiving Q4W treatment) for a minimum of 2 hours after study drug administration. Vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature) and AEs will be assessed at 30 minutes (±10 minutes) post-injection and then at 2 hours (±15 minutes).
6. Starting at visit 7, study drug will be dispensed to the parents (or caregivers) for the dose that will be administered before the next clinic visit. Parents (or 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 parents (or caregivers) have returned to the site.
7. As per standardized regimen outlined in protocol Section 7.2
8. The type, amount, and potency of topical products used during the study will be recorded. The amount of TCS used will be determined by weighing the tube at each visit through the end of the study.
9. 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, [redacted]), administration of study drug, and assessment of injection pain.
10. The questionnaires will be administered only to the subset of patients or parents/caregivers who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).
11. Refer to protocol Section 8.2.2 for details on who (parent or caregiver) is required to complete the specific questionnaires.

12. DFI is to be completed by parent/caregiver.

13. Injection pain assessment at week 2 will only be performed for patients on Q2W treatment

14. Samples will be collected before the injection of study drug

15. TB testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.

16. Urine pregnancy testing at week 2 will only be performed for patients who receive Q2W treatment.

17. EOT is end of study for patients who enter the OLE.

18. Patients who experience adverse events of special interest related to eye disorders (refer to Protocol Section 9.4.3) will also be referred to an ophthalmologist (preferably with expertise in treating pediatric patients or Cornea and External Eye Disease [‘front-of-the-eye’] subspecialty expert). Further evaluation of these AESIs will be performed including any additional tests, if applicable, as per the discretion of the ophthalmologist.

Footnotes for Schedule of Events Table 2

1. Starting at visit 4, study drug will be dispensed to the parents (or caregivers) for the dose that will be administered before the next clinic visit. Parents (or 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 parents (or caregivers) have returned to the site.
2. 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, [redacted]), administration of study drug, and assessment of injection pain.
3. The questionnaires will be administered only to the subset of patients or parents/caregivers who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).
4. Refer to protocol Section 8.2.2 for details on who (parent or caregiver) is required to complete the specific questionnaires.
5. DFI is to be completed by parent/caregiver.
6. Samples will be collected before the injection of study drug
7. Only for patients who do not enter the OLE.
8. Specific assessments to be performed at the unscheduled visit will depend upon the reason for the unscheduled visit.
9. Patients who experience adverse events of special interest related to eye disorders (refer to Section 9.4.3) will also be referred to an ophthalmologist (preferably with expertise in treating pediatric patients or Cornea and External Eye Disease [‘front-of-the-eye’] subspecialty expert). Further evaluation of these AESIs will be performed including any additional tests, if applicable, as per the discretion of the ophthalmologist.

10.3. Potential Major Protocol Violations

*Note: This is a preliminary list and the final list will be generated prior to database lock.

Category	Description of Protocol Deviation
Inclusion Criteria not met but patient randomized	Male or female not ≥6 to <12 years of age at time of screening visit
Inclusion Criteria not met but patient randomized	No diagnosis of AD according to the American Academy of Dermatology consensus criteria (Eichenfield 2003) at screening visit
Inclusion Criteria not met but patient randomized	Chronic AD not diagnosed at least 1 year prior to the screening visit
Inclusion Criteria not met but patient randomized	IGA <4 at the baseline visit
Inclusion Criteria not met but patient randomized	EASI <21 at the baseline visit
Inclusion Criteria not met but patient randomized	BSA <15% at the baseline visit
Inclusion Criteria not met but patient randomized	Baseline worst itch score weekly average score for maximum itch intensity <4
Inclusion Criteria not met but patient randomized	Without documented recent history (within 6 months before the baseline visit) of inadequate response to topical AD medication(s)
Inclusion Criteria not met but patient randomized	Has not applied a stable dose of topical emollient (moisturizer) twice daily for at least 11 out of 14 doses during the 7 consecutive days immediately before the baseline visit
Inclusion Criteria not met but patient randomized	Not willing and able to comply with all clinic visits and study-related procedures
Inclusion Criteria not met but patient randomized	Patient, either alone or with help of parents/legal guardians, as appropriate, is not able to understand and complete study-related questionnaires
Inclusion Criteria not met but patient randomized	Parent or legal guardian did not provide signed informed consent. Patients have not provided separate informed assent to enroll in the study, and signed and dated either a separate informed assent form (IAF) or the informed consent form (ICF) was not signed by the parent/legal guardian (as appropriate based on local regulations and requirements).
Exclusion Criteria met but patient randomized	Participation in a prior dupilumab clinical study
Exclusion Criteria met but patient randomized	Treatment with a systemic investigational drug before the baseline visit NOTE: Treatment with a systemic investigational drug refers to treatment received in a clinical study with a drug that is not yet available on the market
Exclusion Criteria met but patient randomized	Treatment with a topical investigational drug within 2 weeks prior to the baseline visit
Exclusion Criteria met but patient randomized	Treatment with crisabarole within 2 weeks prior to the baseline visit

Exclusion Criteria met but patient randomized	History of important side effects of medium-potency topical corticosteroids (eg, intolerance to treatment, hypersensitivity reactions*, significant skin atrophy, systemic effects), as assessed by the investigator or patient's treating physician *If a patient has a history of hypersensitivity reaction to any particular TCS, and/or other ingredient in the particular TCS drug product, the patient can still be randomized if the investigator believes the patient can be safely treated during the study with a different TCS drug product that does not have cross-reactivity to the drug product that caused the hypersensitivity.
Exclusion Criteria met but patient randomized	Treatment with a TCI within 2 weeks prior to the baseline visit
Exclusion Criteria met but patient randomized	Having used any of the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment: a. Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, etc) b. Phototherapy for AD
Exclusion Criteria met but patient randomized	Treatment with biologics, as follows: a. Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte and CD 19+ lymphocyte count returns to normal, whichever is longer b. Other biologics: within 5 half-lives (if known) or 16 weeks before the baseline visit, whichever is longer
Exclusion Criteria met but patient randomized	Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit NOTE: For patients who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a pediatrician, whether the administration of vaccine can be postponed until after the end of study, or preponed to before the start of the study, without compromising the health of the patient: • Patients for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study. • Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.
Exclusion Criteria met but patient randomized	Planned or anticipated use of any prohibited medications and procedures during study treatment
Exclusion Criteria met but patient randomized	Body weight <15 kg at baseline – all countries except Germany Body Weight <30 kg for Germany
Exclusion Criteria met but patient randomized	Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit)
Exclusion Criteria met but patient randomized	Regular use (more than 2 visits per week) of a tanning booth/parlor within 8 weeks of the baseline visit
Exclusion Criteria met but patient randomized	Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the baseline visit. NOTE: patients may be rescreened after infection resolves

Exclusion Criteria met but patient randomized	Established diagnosis of a primary immunodeficiency disorder (eg, severe combined immunodeficiency, Wiskott Aldrich Syndrome, DiGeorge Syndrome, X-linked Agammaglobulinemia, common variable immunodeficiency), or secondary immunodeficiency. Patients suspected to have immunodeficiency based on their clinical presentation (history of invasive opportunistic infections eg, tuberculosis, other mycobacterial infections, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, chronic mucocutaneous candidiasis, etc or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immunecompromised status, as judged by the investigator
Exclusion Criteria met but patient randomized	History of past or current tuberculosis or other mycobacterial infection Note: Irrespective of status of treatment or infection resolution. Tuberculosis testing will be performed on a country by country basis according to local guidelines if required by regulatory authorities or ethic committees.
Exclusion Criteria met but patient randomized	Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit
Exclusion Criteria met but patient randomized	With an established diagnosis of hepatitis B viral infection at the time of screening or is positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) at the time of screening NOTE: Patients who have gained immunity for hepatitis B virus infection after vaccination (patients who are HBsAg negative, hepatitis B surface antibody [HBsAb] positive, and HBcAb negative) are eligible for the study.
Exclusion Criteria met but patient randomized	With an established diagnosis of hepatitis C viral infection at the time of screening or is positive for hepatitis C antibody at the screening visit
Exclusion Criteria met but patient randomized	On current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis, or hepatic failure, or has evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal (ULN) during the screening period
Exclusion Criteria met but patient randomized	Presence of any 1 or more of the following abnormalities in laboratory test results at screening: • Platelets ≤100 × 10^3/μL • Neutrophils <1.5 × 10^3/μL • Creatine phosphokinase (CPK) >5 × ULN • Serum creatinine >1.5 × ULN NOTE: If an abnormal value is detected at screening, a repeat test should be performed to confirm the abnormality. Only if the repeat test confirms the abnormality, the patient would be categorized as a screen failure.
Exclusion Criteria met but patient randomized	Presence of skin comorbidities that may interfere with study assessments. This includes, but is not limited to, conditions like scabies, seborrheic dermatitis, cutaneous T cell lymphoma, psoriasis, etc.
Exclusion Criteria met but patient randomized	History of malignancy before the baseline visit
Exclusion Criteria met but patient randomized	Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization

Exclusion Criteria met but patient randomized	Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to patients with short life expectancy, patients with uncontrolled diabetes (hemoglobin A1c ≥9%), patients with cardiovascular conditions (eg, Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRF], etc).
Exclusion Criteria met but patient randomized	Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRF, etc.).
Exclusion Criteria met but patient randomized	Planned major surgical procedure during the patient's participation in this study
Exclusion Criteria met but patient randomized	Patient or his/her immediate family is a member of the dupilumab investigational team
Exclusion Criteria met but patient randomized	Patient is female who is pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study
Exclusion Criteria met but patient randomized	Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
Exclusion Criteria met but patient randomized	Patient is female of childbearing potential* and sexually active, who is unwilling to use highly effective methods of contraception prior to the initial dose, during the study and for at least 12 weeks after the last dose of study drug. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, vaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**. * For the purpose of this study, any female who has had her first menstrual period (menarche) and is sexually active will be considered to be of childbearing potential. Female patients who are not of childbearing potential at the start of the study but have the onset of menarche during the course of the study and are sexually active will also have to follow adequate birth control methods to continue participation in the study. ** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. NOTE: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.
Visit not performed	Visit 2 not performed (TCS Standardization)
Visit not performed	Visit 3 not performed (Baseline)

Visit not performed	Visit 19 not performed (End of Treatment)
Visit not performed	Early Termination visit not performed (PD not applicable for patients who completed EOT and rolled over to OLE)
Procedure not performed	IGA not performed at Screening, Baseline/Day 1 or Visit 19/EOT
Procedure not performed	EASI not performed at Screening, Baseline/Day 1 or Visit 19/EOT
Procedure not performed	BSA not performed at Screening or Baseline/Day 1
Procedure not performed	Physical Examination not performed at Screening
Procedure not performed	Electrocardiogram not performed at Screening
Procedure not performed	Serum Pregnancy testing not performed at Screening (must check WOCB at Screening visit: if Yes, for WOCB then must have results)
Procedure not performed	Urine Pregnancy testing not performed at Baseline, Visits 5, 7, 11, 15, 22/EOS or ET (must check WOCB at Screening visit: if Yes, for WOCB then must have results). Major if no pregnancy performed at all. Minor if serum performed instead of urine per protocol.
Procedure not performed	HIV, HBsAg, HBsAb, HBcAb and Hepatitis C Ab not performed at Screening visit
Procedure not performed	Hematology not performed prior to treatment with study drug at Baseline/V3
Procedure not performed	Chemistry not performed prior to treatment with study drug at Baseline/V3
Procedure not performed	Medical History information not collected at Screening
Procedure not performed	Prior Atopic Dermatitis history information not collected at Screening
Procedure not performed	Ophthalmology Exam not performed during Screening period for patients with history of conjunctivitis, blepharitis, or keratitis with 12 months of screening.
Procedure not performed	Any dose missed for non safety-related reasons for patients on Q4W.
Procedure not performed	> 1 dose missed for non safety-related reasons for patients on Q2W
Dosing non compliance	Study drug given to subject without being randomized
Prohibited medications	Treatment with Live (attenuated) vaccine during the study. Examples in section 7.8.1 of the protocol
Prohibited medications	Treatment with Immunomodulating biologics during the study
Prohibited medications	Treatment with an investigational drug (other than dupilumab) during the study
Prohibited medications	Treatment with systemic nonsteroid immunosuppressant during the study. (may be used as rescue, see section 7.3 of protocol for details)
Prohibited medications	Treatment with systemic corticosteroids during the study. (may be used as rescue, see section 7.3 of protocol for details)
Prohibited medications	Treatment with crisabarole during the study.
Prohibited medications	Treatment with TCI Note: The use of TCI is prohibited during the 2-week standardization period leading up to the baseline visit, and the treatment and follow-up periods
Prohibited medications	Treatment with high-potency or very high potency TCS, (high potency TCS may be used as rescue, see Section 7.3 for details)
Prohibited medications	Initiation of treatment of AD with prescription moisturizers
Prohibited procedures	Major elective surgical procedures
Prohibited procedures	Tanning in a bed/booth
Prohibited procedures	Phototherapy (UVA, UVB, nbUVB, high dose UVA and PUVA)
Other: Randomization	Mis-stratification of subject due to incorrectly entered weight group in IVRS

Handling of Investigational Product was not performed in accordance with the protocol	IP has been destroyed without having an approval from the sponsor
Handling of Investigational Product was not performed in accordance with the protocol	Decision to unblind the IP treatment assignment has been made by an unauthorized personnel
Handling of Investigational Product was not performed in accordance with the protocol	Patient was dosed with IP that had a temperature excursion and deemed unacceptable
Inadequate Informed Consent administration	Incorrect ICF (unapproved version, incorrect version, incorrect study, not subject's language)
Inadequate Informed Consent administration	ICF not signed by subject/parent, ICF not dated by subject/parent (incomplete date) or initialed (if applicable). Consent and/or assent not obtained.
Inadequate Informed Consent administration	ICF signed after screening or any study procedures
Inadequate Informed Consent administration	Subject did not re-consent on new version(s) of ICF (to be done by the next following visit)
Inadequate Informed Consent administration	ICF missing for sub-study and DNA sample collected in the presence of a sample
Inadequate source documents	Subject laboratory not reviewed to confirm eligibility by PI
Personnel not qualified and/or designated to perform study-related activities.	Subject confidentiality not maintained
Personnel not qualified and/or designated to perform study-related activities.	Improper delegation of duties
Personnel not qualified and/or designated to perform study-related activities.	Site staff not properly trained to conduct study
Personnel not qualified and/or designated to perform study-related activities.	Staff inappropriately unblinded to study drug arm (except EU sites where unblinded information can be provided base on country requirements)
Randomization error-Subject Randomized to wrong treatment	Subject was randomized and treated with study drug from the incorrect treatment group
Randomization error-Subject Randomized to wrong treatment	Ineligible subject randomized/enrolled

Other: Safety monitoring after study drug	Study drug overdose has not been reported to the sponsor per protocol requirements
Other: Safety monitoring after study drug	Pregnancy has not been reported to sponsor per protocol requirements
Other: Laboratory	Expired lab kits used
Other: Laboratory	Pregnancy test; HIV; HBsAg; HBsAb; Hep C lab results unable to be analyzed to determine eligibility prior to treatment with study drug at Baseline/V3
Other: Laboratory	Hematology or Chemistry lab samples were unable to be analyzed to determine eligibility prior to treatment with study drug at Baseline/V3
Other: AESI	AESI not reported within protocol defined window
Other: SAE	SAE not reported within protocol defined window

10.4. Criteria for Treatment-Emergent Potentially Clinical Significant Value for Pediatric Patients (>=6 to <11 years old)

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 and 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.

[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
Creatinine	≥90µmol/L and baseline < 90µmol/L (or ≥1.1 mg/dL and baseline <1.1 mg/dL) >=30% change from baseline	Benichou C., 1994 Two independent criteria
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)	

Parameter	Treatment Emergent PCSV[1]	Comments
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)	
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	<5.0 Giga/L and ≥5.0 Giga/L at baseline >17.0 Giga/L and ≤17.0 Giga/L at baseline	
Lymphocytes	<1.0 Giga/L and ≥1.0 Giga/L at baseline >8.0 Giga/L and ≤ 8.0 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	>0.7 Giga/L and <= 0.7 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) or any decrease ⩾ 2 g/dL ≥20 g/dL and <20 g/dL at baseline (or >=200 g/L and <200 g/L at baseline)	Two criteria are independent .
Hematocrit	< 32% and ≥ 32% at baseline >47% and ≤ 47% at baseline	Two Criteria are independent

Parameter	Treatment Emergent PCSV[1]	Comments
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
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	≤80 mmHg and decrease from baseline ≥ 20mmHg ≥108 mmHg and increase from baseline ≥ 20mmHg	
DBP	≤48 mmHg and decrease from baseline ≥ 10mmHg ≥72 mmHg and increase from baseline ≥ 20mmHg	
Temperature	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary: >99 °F/37.2 °C	
Respiratory rate	<16 per minute and ≥16 per minute at baseline >30 per minute and ≤30 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	≥170 ms and <170 ms at baseline	
QRS	≥100 ms and <100 ms at baseline	

Parameter	Treatment Emergent PCSV[1]	Comments
QTc	Absolute values (ms) Borderline: 431-450 ms and < 431ms at baseline Prolonged: >450 ms and ≤ 450 ms at baseline Additional: ≥500 ms and < 500 ms at baseline	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)
	AND	To be applied to QTcF; QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual patient listings
	Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	Independent criteria

10.5. 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 and Severity = "severe" - HLT = Allergies to foods, food additives, drugs and other chemicals and Severity = "severe" or Serious="Yes" 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

10.6. 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

   b. Never considered rescue

   - ATC2 = EMOLLIENTS AND PROTECTIVES
   - ATC2 = VASOPROTECTIVES
   - ATC2 = ANALGESICS
   - ATC2 = ANTI-ACNE PREPARATIONS
   - ATC2 = TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
   - ATC2 = ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
   - ATC2 = ANTIVIRALS FOR SYSTEMIC USE
   - ATC2 = ANTIFUNGALS FOR DERMATOLOGICAL USE
   - ATC2 = ANTISEPTICS AND DISINFECTANTS
   - ATC2 = ANTIHISTAMINES FOR SYSTEMIC USE
   - ATC2 = ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.
   - ATC2 = GENERAL NUTRIENTS
   - ATC2 = VITAMINS
   - ATC2 = DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
   - ATC2 = OPHTHALMOLOGICALS
   - ATC2 = ANTIINFLAMMATORY AND ANTIRHERUMATIC PRODUCTS
   - ATC2 = PSYCHOLEPTICS
   - ATC4 = CORTICOSTEROIDS, WEAK (GROUP I)

- ATC1 = ANTIINFECTIVES FOR SYSTEMIC USE
- ATC1 = BLOOD AND BLOOD FORMING ORGANS
- ATC1 = ALIMENTARY TRACT AND METABOLISM
- ATC1 = MUSCULO-SKELETAL SYSTEM
- ATC2 = COUGH AND COLD PREPARATIONS
- Preferred Drug Name = TRIAMCINOLONE ACETONIDE

[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.

1. **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

10.7. PROMIS Scoring Tables

Anxiety 8a - Pediatric v2.0		
Short Form Conversion Table		
Raw Score	T-Score	SE*
8	33.5	5.9
9	38.0	4.9
10	40.6	4.7
11	43.0	4.4
12	44.9	4.2
13	46.7	4.0
14	48.3	3.9
15	49.8	3.8
16	51.2	3.8
17	52.5	3.7
18	53.8	3.7
19	55.1	3.7
20	56.3	3.7
21	57.5	3.7
22	58.7	3.7
23	59.9	3.7
24	61.0	3.7
25	62.2	3.7
26	63.4	3.7
27	64.5	3.7
28	65.7	3.6
29	66.9	3.6
30	68.1	3.6
31	69.3	3.7
32	70.6	3.7
33	71.8	3.7
34	73.2	3.7
35	74.6	3.8
36	76.0	3.8
37	77.6	3.9
38	79.3	4.0
39	81.1	3.9
40	83.3	3.8

SE* = Standard Error on T-Score

Pediatric v2.0 - Depressive Symptoms 8a		
Short Form Conversion Table		
Raw Score	T-Score	SE*
6	36.2	5.9
7	42.1	4.4
8	45.4	4.0
9	48.0	3.6
10	50.2	3.4
11	52.1	3.3
12	53.9	3.2
13	55.6	3.1
14	57.2	3.1
15	58.9	3.1
16	60.5	3.1
17	62.1	3.1
18	63.7	3.1
19	65.3	3.1
20	66.8	3.1
21	68.4	3.1
22	70.0	3.1
23	71.5	3.0
24	73.1	3.0
25	74.7	3.0
26	76.3	3.1
27	78.1	3.2
28	80.2	3.3
29	82.5	3.4
30	84.7	3.2

SE* = Standard Error on T-Score

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ESig Approval	[redacted]gement 10-May-2019 14:29:14 GMT+0000

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