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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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

Compound:	Dupilumab
Clinical Phase:	3
Protocol Number:	R668-AD-1652
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[redacted]

AMENDMENT HISTORY

Amendment 3

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Due to an inadvertent operational error, 68 patients were potentially unblinded. In order to properly power for a sensitivity analysis for the subset of patients who were not potentially unblinded, additional patients will be enrolled and randomized. Included introduction of the modified full analysis set (mFAS), which excludes potentially unblinded patients, and will be used for sensitivity analysis. Stated that potentially unblinded patients will be excluded from the per protocol set (PPS). Added power calculation for the full analysis set (FAS) with the additional patients.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Population Clinical Study Protocol Synopsis: Statistical Plan – Sample Size Consideration, Efficacy Analysis Sets Section 5.1 Study Description and Duration Figure 1 Study Design Section 6.1 Number of Patients Planned Section 7.6 Method of Treatment Assignment Section 10.2 Justification of Sample Size Section 10.3.1 Efficacy Analysis Sets Section 10.4 Patient Disposition Section 10.5.2 Efficacy Analyses
Extended the duration of the visit window between Visit 1 and Visit 2 from 21 days to 63 days (ie, changed start of Visit 1 from -35 days to -77 days) and removed the limit of rescreen once to allow for the seamless screening/enrolment of all new patients into the study. This was considered necessary to remain compliant with Good Clinical Practice (GCP) regulations regarding enrolment practices until approval of this protocol amendment.	Clinical Study Protocol Synopsis: Study Design Section 5.1 Study Description and Duration, Figure 2 Section 6.2.1 Inclusion Criteria, #7 Section 8.1 - Table 1 Schedule of Events (Screening, TCS Standardization, Baseline, and Treatment Period)
Revised Inclusion Criterion #9: At least 11 (of a total of 14) applications of a stable dose of topical emollient (moisturizer) during the 7 consecutive days immediately before the baseline visit. The criterion prior to this amendment requiring 100% compliance with application of a stable dose of topical emollient twice daily for the entire 7 consecutive days immediately before the baseline visit is overly restrictive for this patient population. This change would ensure that pediatric patients do not unnecessarily screen fail entry into this study.	Clinical Study Protocol Synopsis: Background Treatment Section 5.1 Study Description and Duration Section 6.2.1 Inclusion Criteria, #9 Section 7.2 Background Treatment

Change	Section Changed
Added rationale for the inclusion of a placebo treatment group in the study design and a description of the risks and benefits to patients assigned to the placebo treatment group. This change had previously been requested by the Czech Republic (Czechia) regulatory agency and had been included in a country-specific amendment, but it is now being incorporated into the global protocol.	Section 3.2.1 Rationale for Study Design
Added a benefit-risk section for treatment of atopic dermatitis with dupilumab. This change had previously been requested by the Czechia regulatory agency and had been included in a country-specific amendment, and is now being incorporated into the global protocol. The section summarizes relevant previous Regeneron studies. It notes that the safety profile was consistent between pediatric and adult populations, and that dupilumab was efficacacious in all previous Regeneron trials.	New Section 3.2.4, Section 3.2.4.1, Section 3.2.4.2, and Section 3.2.4.3
Revised Figure 1 and its title to clarify that patients randomized to dupilumab Q4W receive 300 mg dupilumab regardless of body weight (Arm B).	Section 5.1 - Figure 1 Study Design
Corrected the description of age limit of the study population from “aged ≥6 to <12 years at the time of baseline” to “aged ≥6 to <12 years at the time of screening” to be consistent with the wording in the Inclusion Criteria and other sections of the protocol.	Section 6.2 Study Population
Revised language for accelerated reporting of pregnancy to sponsor and the duration patients who are female of childbearing potential and sexually active are required to use highly effective methods of contraception after the last dose of study drug, to align with the current dupilumab label.	Section 6.2.2 Exclusion Criteria, #31 Section 9.4.3 Other Events that Require Accelerated Reporting
Added body temperature to the list of post-dose vital signs to be assessed.	Section 7.1 Investigational and Reference Treatments Table 1 Schedule of Events (Screening, TCS Standardization, Baseline, and Treatment Period) (Added footnote “5” to the row “Study drug administration (patients receiving Q4W treatment)” for visits 3, 7, and 11 Section 8.1.1.1 Footnotes for Schedule of Events Table 1 (footnote 5)

Change	Section Changed
Revised text to emphasize that the use of very-high-potency topical corticosteroids (TCS) is prohibited during the study, as their use is not recommended in patients under 12 years of age. Also included examples of very-high-potency TCS.	Section 7.2 Background Treatment (6th bullet) Section 7.3 Rescue Treatment Section 7.4.2.1 Reason for Permanent Discontinuation of Study Drug Section 7.8.1 Prohibited Medications and Procedures (8th bullet)
Included "injection observation" for the every 4 week regimen in the Schedule of Events table, to identify the visits at which the observation occurs.	Section 8.1 - Table 1 Schedule of Events (Screening, TCS Standardization, Baseline, and Treatment Period)
Removed Footnote #18 (shown below) in the row for Ophthalmology Exam in the Schedule of Events table. "In the event the ophthalmology examination cannot be performed within the 35-day screening visit window 1 the screening period can be extended by 4 weeks; however, the 14-day interval between visits 2 and visits 3 may not be extended." The rationale for removing this footnote is that all patients will now have an additional 4 weeks of screening.	Section 8.1 - Table 1 Schedule of Events (Screening, TCS Standardization, Baseline, and Treatment Period) Section 8.1.1.1 Footnotes for Schedule of Events Table 1, original #18 (removed)
Revised the adverse events of special interest definition for conjunctivitis, keratitis, and blepharitis. It originally read: Conjunctivitis (any type or etiology), keratitis, or blepharitis (only events that are either severe or serious or lasting ≥4 weeks will be reported as AESIs). The criteria "or lasting ≥4 weeks" was removed. In previous dupilumab trials for the treatment of atopic dermatitis, including one in adolescent patients, events of mild to moderate severity were not found to be clinically meaningful, even when lasting >28 days during the study, as they did not result in sequelae or treatment discontinuation.	Section 9.4.3 Other Events that Require Accelerated Reporting
Specified the list of potential major protocol violation types for the PPS, per request from the United States Food and Drug Administration.	Clinical Study Protocol Synopsis: Statistical Plan – Efficacy Analysis Sets Section 10.3.1 Efficacy Analysis Sets Appendix 3 Potential Major Protocol Violations (added)
Revision was made to clarify that the hierarchical testing order for the primary endpoint and key secondary endpoints is shown in Table 3 is an abbreviated, preliminary plan as it is stated that the complete hierarchy including all the secondary endpoints will be provided in the statistical analysis plan (SAP).	Section 10.5.2.1 Multiplicity Considerations, Table 3

Amendment 2

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Corrected the header to read R668-AD-1652 versus R668-AD-1526.	Section 8.1 Schedule of Events (Screening, TCS Standardization, Baseline, and Treatment Period) Table 1

Amendment 1

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Modified the other secondary endpoint of "Mean weekly dose of TCS in grams potency TCS from baseline to week 16" to include low-potency TCS	Section 4.2.2 Secondary Endpoints Synopsis
As per regulatory agency request, added inclusion criteria #7 for Baseline worst itch score	Section 6.2.1 Inclusion Criteria
Revised exclusion criteria #21: Children who are engaging in heavy exercise can have transient increases in CPK that are not clinically relevant.	Section 6.2.2 Exclusion criteria Section 7.4.2.2 Reasons for Temporary Discontinuation of Study Drug
Clarified the text indicating where moisturizers should be applied by the deletion of the following text in the third sentence "on the are(s) of nonlesional skin designated for such assessments"	Section 7.2 Background Treatment
Modified the reporting schedule for patient assessment of pruritus. Patients will answer both questions in the evening.	Section 8.2.2.1 Patient Assessment of Pruritus Using Worst Itch Scale
Deleted "alcohol and drug drug screen test" under "**Other Laboratory Tests**" and throughout the protocol.	Section 8.2.3.5 Laboratory Testing Section 8.2.1 Procedures Performed only at the Screening/Baseline Visit
Updated this section to delete the reference to region-specific, allergen- specific IgE as this is not being collected.	Section 8.2.5 Biomarker Procedures

Change	Section Changed
As per regulatory agency request, added an Ophthalmological Examination section for patients who have history of certain eye disorders (conjunctivitis, blepharitis or keratitis) within the last 12 months and patients who experience adverse events of special interest related to eye disorders. Certain types of eye disorders (conjunctivitis, blepharitis, keratitis) are adverse events of special interest for the study drug. Including referral to a specialist will allow a more robust and comprehensive evaluation of baseline disease status of patients with history of these disorders, as well as of any treatment emergent adverse events falling under this category.	Section 8.2.3.6 Ophthalmological Examination
Added the Mantel-Fleiss (MF) criterion. If it is not met, sensitivity analyses including each factor separately in CMH test will be conducted.	Section 10.5.2.1 Primary Efficacy Analysis Synopsis
Added other secondary endpoints: • 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 at week 16 • Time to onset of effect on pruritus during the 16-week treatment period (≥4 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) As per regulatory agency request, added additional details regarding the multiple imputation procedure.	Section 6.2.1 Inclusion criteria Section 4.2.2 Secondary Endpoints Section 10.5.2.2.Secondary Efficacy Analysis Synopsis
As per regulatory agency request, added the hierarchical testing order for the primary endpoint and key secondary endpoints	Section 10.5.2.3 Multiplicity Considerations
Added the Investigator's Global Assessment (IGA) scale to the protocol. The scale was already included in the efficacy procedures and in the Study Manual and was added to Appendix 2 for further clarification.	Appendix 2 IGA Scale

Change	Section Changed
Minor editorial changes	Cover page: Updated the name of the Scientific/Medical Monitor: Section 8.1 Schedule of Events (Screening, TCS Standardization, Baseline, and Treatment Period) Table 1 Section 8.1.1.1 Footnotes for Schedule of Events Table 1 Section 8.1 Schedule of Events (Follow-Up Period, Unscheduled Visits, and Early Termination) Section 8.1.1.2 Footnotes for Schedule of Events Table 2 Section 8.2.2.9 Investigator's Global Assessment Section 8.2.5 Biomarker Procedures

CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Locations	Multiple sites in North America and the European Union (EU).
Principal Investigator	To be determined
Objectives	**The primary objective** of the study is to demonstrate the efficacy of dupilumab administered concomitantly with topical corticosteroids (TCS) in patients ≥6 years to <12 years of age with severe atopic dermatitis (AD). **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.
Study Design	This is a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of dupilumab administered concomitantly with TCS in pediatric patients with severe AD. 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 randomized to 1 of the following treatment groups: • dupilumab every 2 weeks (Q2W) treatment group: 100 mg for patients <30 kg or 200 mg for patients ≥30 kg • dupilumab every 4-weeks (Q4W) treatment group: 300 mg • placebo group The study will consist of the following periods: screening of up to 9 weeks, a TCS standardization period of 2 weeks, treatment period of 16 weeks, and a follow-up period of 12 weeks. After the parents or legal guardians provide an informed assent (as appropriate), 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 will be permitted during the screening period at the discretion of the investigator. Starting on day -14, all patients will initiate a standardized TCS treatment regimen and will continue this regimen through the end of the study. Patients may be rescreened, unless the reason for the screen failure is related to failing the disease severity inclusion criteria. Patients should apply moisturizers twice daily for at least 7 days before randomization and continue throughout 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 weight group (<30 kg and ≥30kg) and region (North America/Europe) as follows: • dupilumab Q2W treatment group: Patients with baseline weight <30 kg will receive Q2W subcutaneous (SC) injections of 100 mg dupilumab 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 following a loading dose of 400 mg on day 1 • dupilumab Q4W treatment group: Patients regardless of weight will receive Q4W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1. • placebo treatment group: Patients will receive 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). During the treatment period, patients will have weekly in-clinic visits through week 4, then every 4 weeks in-clinic visits through week 16, with weekly telephone visits in between in-clinic visits. Parents/caregivers will be trained on injecting study drug during in-clinic visit 3 (day 1) to visit 7 (week 4). 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. The end of treatment period visit will occur at week 16. The co-primary endpoints will be assessed at this visit. Patients who participate in the study may subsequently be eligible to participate in an open-label extension (OLE) study.
Study Duration	The duration of the study for each patient is approximately 16 weeks, excluding the screening period, for patients entering the OLE and 28 weeks, excluding the screening period for patients who decline to enter the OLE.

Population	
Sample Size:	Approximately 330 patients are planned to be enrolled into 3 groups: dupilumab Q2W treatment group (100 mg Q2W or 200 mg Q2W), dupilumab Q4W treatment group (300 mg Q4W), or placebo group.
Target Population:	The study population includes pediatric patients (aged ≥6 to <12 years at the time of screening) who have severe AD that cannot be adequately controlled with topical AD medications.
Treatments	
Study Drug	Dupilumab will be given Q2W or Q4W:
Dose/Route/Schedule:	• dupilumab Q2W treatment: o SC injections of dupilumab, 200 mg loading dose on day 1, then 100 mg Q2W from week 2 to week 14, or o SC injections of dupilumab, 400 mg loading dose on day 1, then 200 mg Q2W from week 2 to week 14 • dupilumab Q4W treatment: SC injections of dupilumab, 600 mg loading dose on day 1, then 300 mg Q4W from week 4 to week 12.
Placebo **Route/Schedule:**	3 matching placebo formulations (without addition of active substance) will be used during the study: 1. 2 mL placebo matching 300 mg dupilumab 2. 1.14 mL placebo matching 200 mg dupilumab formulation 3. 0.7 mL placebo matching 100 mg dupilumab SC injections of placebo matching dupilumab Q2W (100 and 200 mg) or Q4W (300 mg) (including doubling the amount of placebo on day 1 to match the loading dose).
Background Treatment **Dose/Route/Schedule:**	All patients should apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization and are to continue to apply moisturizers throughout the study (all 28 weeks where applicable). However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of nonlesional skin designated for such assessments for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers (eg, ceramide containing products like epiceram®) or moisturizers containing additives (ceramide, hyaluronic acid, urea, filaggrin degradation products) during the screening period or during the study. Patients may continue using stable doses of such moisturizers if initiated before the screening visit. Starting on day -14, all patients will initiate a standardized TCS treatment regimen and will continue this regimen through the end of the study.

Endpoints

Primary :	• Proportion of patients with Investigator's Global Assessment (IGA) 0 or 1 (on a 5-point scale) at week 16
Co-primary (for European Medicines Agency (EMA) and EMA Reference Market Countries Submissions):	• Proportion of patients with Eczema Area and Severity (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
Secondary:	**Key Secondary Endpoints:** • 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 **Other Secondary Endpoints:** • 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 Body Surface Area (BSA) affected by AD • Percent change from baseline to week 16 in SCORing AD (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 at 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 Children's Dermatology Life Quality Index (CDLQI) • Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM) • Change from baseline to week 16 in Dermatitis Family Index (DFI)

	• Change from baseline to week 16 in Patient-Reported Outcomes Measurement Information System (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- and 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 treatment-emergent adverse events (TEAEs) (excluding herpetic infections) through week 16 • Incidence of serious TEAEs through week 16
Procedures and Assessments	Efficacy will be assessed during the study at specified clinic visits using patient-reported assessments (including worst itch score, patient global impression of disease, patient global impression of change, CDLQI, POEM, DFI, Patient Reported Outcomes Measurements Information Systems (PROMIS) anxiety and depression scores, Faces pain scale, and investigator-reported assessments (including BSA affected by AD, SCORAD, Global Individual Signs Score [GISS], and EASI that measure the extent and severity of AD, and the IGA that rates the overall severity of AD). Safety will be assessed by vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and clinical evaluations. Patients will be asked to monitor all adverse events (AEs) experienced from the time of informed consent/assent until their last study visit.

Statistical Plan

Sample Size Consideration:

Based on the initial sample size of 240 patients (prior to this amendment), it is estimated that with 80 patients per group, at the 2-sided 5% significance level, the study will have:

- 97% power to detect a difference of 23% between dupilumab Q2W treatment and placebo treatment (both in combination with TCS) in the percentage of patients who achieve an IGA score 0 or 1 at week 16, assuming that the percentages are 28% and 5% for dupilumab Q2W and placebo, respectively
- 87% power to detect a difference of 17% between dupilumab Q4W treatment and placebo treatment (both in combination with TCS) in the percentage of patients who achieve an IGA score 0 or 1 at week 16, assuming that the percentages are 22% and 5% for dupilumab Q4W and placebo, respectively
- 99% power to detect a difference of 51% in the percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 68% and 17% for dupilumab Q2W and placebo, respectively, (both in combination with TCS)
- 99% power to detect a difference of 45% in percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 62% and 17% for dupilumab Q4W and placebo, respectively, (both in combination with TCS)

Due to an inadvertent operational error, 68 patients were potentially unblinded. Details about the error and why it may have been unblinding are not included in the protocol but will be described in the clinical study report. An additional approximately 90 patients will be 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.

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

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 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.

Analysis Methods:

Primary Efficacy Analyses

The Cochran-Mantel-Haenszel test adjusted by randomization strata (baseline weight group and region) will be used for analyzing the 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 checked, and if it is not met, sensitivity analyses including each stratification factor separately in CMH test will be conducted.

To account for the impact of rescue treatment on the efficacy effect: For the primary efficacy endpoints (which are binary efficacy endpoints), if rescue treatment is used, the patient will be classified as a nonresponder from the time the rescue is used.

If a patient withdraws from study, this patient will be counted as a nonresponder for endpoints after withdrawal.

Sensitivity analysis using the last observation carried forward (LOCF) approach 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. The efficacy data will be set to missing after rescue treatment is used, then the LOCF method will be used to determine patients' status at week 16.

In addition, the Cochran-Mantel-Haenszel method adjusted by randomization strata will also be performed on all observed data regardless if rescue treatment is used. A patient with missing data will be counted as a non-responder. Other sensitivity analyses may be conducted.

Secondary Efficacy Analyses

For binary endpoints, the secondary efficacy analysis will use the same approach as that used for the primary analysis.

For continuous endpoints:

- The multiple imputation (MI) with analysis of covariance (ANCOVA) model will be used for analysis. Missing data from the FAS will be imputed 40 times to generate a complete dataset at each imputation by using the MI Statistical Analysis System (SAS) procedure. These complete datasets will be analyzed using an ANCOVA model with treatment, randomization strata (region and weight group) and relevant baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula.
- To account for the impact of rescue treatment on the efficacy effect: If a patient receives rescue treatment, the efficacy data collected after rescue treatment is initiated will be treated as missing.
- In addition to the MI method described previously, sensitivity analyses such as ANCOVA model with LOCF and MI method with ANCOVA model on all observed data regardless of rescue use will be conducted. Additional details on these sensitivity analyses will be provided in the statistical analysis plan (SAP).

Multiplicity Consideration

A hierarchical procedure for multiplicity adjustment 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. The hierarchical testing procedure at the 2-sided 0.05 significance level will be used for all comparisons with the placebo.

Safety Analyses

Safety analysis will be based on the SAF. This includes reported TEAEs and other safety information (eg, clinical laboratory evaluations, vital signs, and 12-lead ECG results).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ARISg	Pharmacovigilance and clinical safety software system
AST	Aspartate Aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
CDLQI	Children's Dermatology Life Quality Index
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
DFI	Dermatitis Family Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
FAS	Full analysis set
GCP	Good Clinical Practice
GISS	Global Individual Signs Score
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IAF	Informed assent form
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4Rα	IL-4 receptor alpha subunit

IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web responses system
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
MI	Multiple imputation
NAb	Neutralizing antibody
NRS	Numerical Rating Scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PROMIS	Patient Reported Outcomes Measurements Information Systems
PT	Preferred term
QOL	Quality of life
QW	Once a week
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION

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 (Bieber 2008).

Atopic dermatitis is one of the most common skin disorders in infants and children (Mortz 2015). The disease affects over 20% of children in many industrialized countries (Deckers 2012). 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 (Kay 1994). 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 (Asher 2006). 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% (Laughter 2000).

The clinical pattern of AD varies with age. Infants typically present with erythematous papules and vesicles on the cheeks, forehead, or scalp, which are exudative and intensely pruritic. The childhood phase typically occurs from 2 years of age to puberty. Children present with lichenified papules and plaques representing the more chronic disease involving the hands, feet, wrists, ankles, and antecubital and popliteal regions. In adults, predominant areas of involvement include the flexural folds, the face and neck, the upper arms and back, and the dorsa of the hands, feet, fingers, and toes. The eruption is characterized by dry, scaling erythematous papules and plaques, and the formation of large lichenified plaques from lesional chronicity.

The disease has been shown to have a marked impact on the quality of life (QOL) of pediatric patients, greater than that seen in other common skin disorders like psoriasis and urticaria (Beattie 2006). A study comparing the impact on the QOL of family members of children suffering from eczema and type 1 diabetes found that all families of children with moderate to severe eczema had significantly higher impact scores than those of diabetic children (Su 1997). Often severe, pruritus is a universal finding in AD and often results in sleep disruption, irritability, and generalized stress for both the affected patients as well as family members (Kim 2012).

Of particular interest in children is the phenomenon of "Atopic March" which is characterized by a typical sequence of progression of clinical signs of atopic disease. In general, the clinical signs of AD and of food allergies predate the development of asthma and allergic rhinitis, suggesting that AD is an "entry point" for subsequent allergic disease (Spergel 2003). Severity of AD is correlated with development of asthma and allergic rhinitis (Zheng 2011). The prevalence of asthma in children 6 years and older who had developed eczema during the first 4 years of their life has been estimated to be around 35% (Van der Hulst 2007). In a prospective study on 'Atopic March' in which children with eczema during infancy were followed, 47% of patients had allergic rhino-conjunctivitis and 29% had asthma (Ekback 2014) by the age of 10 years. More severe skin disease is directly correlated with a higher risk of developing comorbidities (asthma, allergic rhinitis, food allergy, and mental health disorders) and is associated with more severe comorbidities (Silverberg 2013). The incidence of mental health disorders like anxiety,

depression, and Attention Deficit Hyperactivity Disorder (ADHD) is also higher in children with AD (Yaghmaie 2013). The course of the disease in school-going children can be complicated by potentially life-threatening complications like eczema herpeticum (Luca 2012).

Atopic dermatitis is caused by a complex interaction of genetics, defects in skin barrier function, environmental exposure, and immunologic responses. Type 2 helper T cell (Th2)-mediated immune response is believed to play a central role in the pathogenesis of AD. The skin lesions of AD are characterized by increased expression of proinflammation Th2 cytokines, such as interleukin (IL)-4 and IL-13, and by skin infiltration of Th2 cells. The elevated IgE responses and eosinophilia observed in the majority of patients with AD reflects an increased expression of the Th2 cytokines IL-4 and IL-13 (Leung 1999). Type 2 helper T cell-associated cytokines regulate important barrier-related functions, such as epidermal cornification and production of antimicrobial proteins. These cytokines inhibit the production of major terminal differentiation proteins, such as loricrin, filaggrin, involucrin, and the antimicrobial proteins human beta defensin 2 and 3, which in turn, is associated with development of AD (Howell 2007, Guttman-Yassky 2011a, Guttman-Yassky 2011b). The Th2 cytokines also act on keratinocytes and induce production of chemokines, including chemokine (C-C motif) ligand 17 (also known as thymus and activation-regulated chemokine [TARC]), and chemokine (C-C motif) ligand 26 (also known as eotaxin-3), which are chemo-attractants for Th2 cells and eosinophils, thus, perpetuating the inflammatory response. Since activation of IL-4 and IL-13 signaling precedes the release of proinflammatory mediators, antagonism of these cytokines has the potential to reduce the Th2 response and provide therapeutic benefit.

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 (Proudfoot 2013). 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 (Schmitt 2009).

Dupilumab is a novel targeted immunoregulatory agent that selectively and simultaneously inhibits IL-4 and IL-13 signaling through the IL-4 receptor alpha subunit (IL-4Rα) by binding to the obligate shared component (IL-4Rα) of the IL-4/IL-13 receptor complex. It is intended to inhibit key disease drivers to achieve clinical benefit without the side effects commonly observed with existing non-selective systemic immunosuppressants. Dupilumab, given subcutaneously (SC), is currently in clinical trials for multiple indications, including treatment of moderate-to-severe AD in patients intolerant of, or whose disease is not adequately controlled with, topical treatments.

Overall, 7408 subjects have been enrolled into the dupilumab development program (completed and ongoing studies) as of 30 September 2016: 222 healthy volunteers, 4182 patients with AD, 2909 patients with asthma, 60 patients with nasal polyposis, and 35 patients with eosinophilic esophagitis. In completed or unblinded studies, 3927 subjects have received dupilumab: 202 healthy volunteers, 2853 patients with AD, 842 patients with asthma and 30 patients with nasal polyposis. Taking into account patients exposed to dupilumab in blinded studies, the total number of patients exposed to dupilumab is over 5,000.

Further, 1 clinical study with dupilumab in the pediatric population has been completed at the time of this protocol development; a phase 2 study (R668-AD-1412) investigating the safety, pharmacokinetics (PK), immunogenicity, and exploratory efficacy of dupilumab in patients aged ≥6 to <18 years with AD, and an open-label extension (OLE) study to assess the long-term safety and efficacy of dupilumab in patients aged ≥6 to <18 years with AD (R668-AD-1434) is ongoing. A total of 78 pediatric patients were exposed to dupilumab at doses of either 2 mg/kg or 4 mg/kg (single dose, weight dependent) followed by 4 weekly doses of 2 mg/kg or 4 mg/kg (weight-dependent, once a week [QW] regimen). The safety data gathered from these pediatric studies are summarized in Section 3.2.3.

A total of 1,379 adult patients with moderate-to-severe AD were enrolled in the identically designed SOLO 1 and SOLO 2 phase 3 adult studies. Patients were enrolled if they were not adequately controlled with topical medications, or if topical treatment was not medically advisable. Patients were randomized into 1 of 3 treatment groups: dupilumab 300 mg SC QW, dupilumab 300 mg SC every 2 weeks (Q2W), or placebo for 16 weeks following an initial dupilumab loading dose of 600 mg SC, or placebo. Results at 16 weeks included the following:

- For SOLO 1 and SOLO 2, respectively, 37% and 36% of patients who received dupilumab 300 mg QW, and 38% and 36% of patients who received dupilumab 300 mg Q2W, achieved clearing or near-clearing of skin lesions (IGA 0 or 1), compared to 10% and 8.5% with placebo ($p<0.0001$). This was the primary endpoint of the study in the US and one of the primary endpoints in the European Union (EU).

- For SOLO 1 and SOLO 2, respectively, 52.5% and 48% of patients who received dupilumab 300 mg QW, and 51% and 44% of patients who received dupilumab 300 mg Q2W, achieved EASI-75 compared to 15% and 12% with placebo ($p<0.0001$). This was the key secondary endpoint in the US and one of the primary endpoints in the EU.

For SOLO 1 and SOLO 2, respectively, the percent improvement in Eczema Area and Severity Index (EASI) from baseline was 72% and 69% in patients who received the 300 mg QW dose, and 72% and 67% for patients who received dupilumab 300 mg Q2W, compared to 38% and 31% for placebo patients ($p<0.0001$).

Nonclinical repeat-dose toxicity studies and reproductive and developmental toxicity studies have shown a lack of any general or reproductive toxicology and postnatal effects observed with anti-IL-4Rα surrogate antibodies in cynomolgus monkeys and mice. These nonclinical data, together with the clinical safety profile of dupilumab to date, support the evaluation of dupilumab in pediatric patients.

Dupilumab was shown to be generally well tolerated with a favorable safety profile in concluded phase 3 studies in adult patients with moderate-to-severe AD (SOLO 1, SOLO 2). The overall incidence of treatment-emergent adverse events (TEAEs) was similar across all treatment groups (300 mg QW, 300 mg Q2W, placebo). The incidence of any treatment-emergent serious adverse event (SAEs) was higher in the placebo groups than in the dupilumab groups. The incidence of any TEAEs leading to permanent treatment discontinuation was similar across all groups. There is no indication that dupilumab treatment increased the incidence of acute allergic reactions overall. The incidence of treatment-emergent adverse events of special interest (AESI) of acute allergic reactions requiring treatment was <1% in dupilumab-treated patients and lower than in placebo-treated patients. In the SOLO studies, there was no report of anaphylaxis or serum sickness in dupilumab-treated patients. There was no increase in infections in general, serious infections, or any of the infection AESIs with dupilumab compared to placebo. Further, the incidence of severe infection and opportunistic infection AESI was higher in placebo-treated patients than in dupilumab-treated patients.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

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.

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.

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

In pediatric patients ≥6 years to <12 years old who are suffering from severe AD that is inadequately responsive to topical therapies (TCS with/without TCIs), treatment with dupilumab, in addition to TCS, will result in clinically relevant and statistically significant incremental benefit versus treatment with TCS alone, as measured by proportion of patients who achieve Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear disease) and Eczema Area and Severity Index (EASI)-75 (at least 75% reduction in EASI score from baseline).

3.2. Rationale

3.2.1. Rationale for Study Design

This study is part of the pediatric clinical development plan for dupilumab in AD. The primary purpose of the study is to provide data on the use of dupilumab concomitantly with TCS to support regulatory approval in patients, ≥6 years to <12 years of age, with severe AD.

Since TCS represent the mainstay of pharmacological treatment of AD, many patients may use dupilumab in combination with TCS. Hence, the use of topical therapy as background medication will allow the study design to reflect more closely the anticipated real-life use of dupilumab. This design seeks to maximize clinical benefit for patients enrolled in the study. Although the target population consists of patients who are inadequately responsive to TCS, these patients are still expected to receive some benefit from the use of TCS. Data from phase 3 studies in adults (R668-AD-1334, R668-AD-1416, and R668-AD-1224) in which dupilumab was evaluated both as monotherapy (R668-AD-1334 and R668-AD-1416) and concomitantly with TCS (R668-AD-1224) showed that for certain clinical endpoints, the combination regimen was more efficacious than monotherapy. Moreover, this design will also generate data on the potential steroid-sparing effect of dupilumab.

The 16-week treatment duration is the same as in 2 of the adult pivotal trials (R668-AD-1416 and R668-AD-1334). This duration has been chosen because it is expected that the vast majority of patients will achieve maximum therapeutic effect for dupilumab by this time. Moreover, in previous studies, the selected dupilumab dose regimens have been shown to achieve steady state concentration before the end of this period. The 12-week follow-up period is based on the expected PK of dupilumab after the last dose, ie, the time for serum concentrations to decline to nondetectable levels (below the lower limit of quantification) in most patients.

The co-primary endpoints chosen in the study (proportion of patients achieving IGA 0 or 1 and proportion of patients with ≥75% reduction in EASI from baseline [EASI-75] at week 16) are the same as those used in the adult pivotal studies (R668-AD-1334 and R668-AD-1416). These endpoints are both investigator-assessed outcome measures of objective AD signs, which are broadly validated in drug development for this indication. Based on prior discussions with health authorities for the pivotal adult AD studies (R668-AD-1334 and R668-AD-1416), it is expected that different health authorities will request different primary endpoints for this study (for example, the US Food and Drug Administration (FDA) requested IGA 0/1 as the primary

endpoint in the adult AD program while European Medicines Agency (EMA) requested both EASI-75 and IGA 0/1 as co-primary endpoints). Eczema Area and Severity Index has been validated in the pediatric population including in patients aged 6 to 11 years old in a prior study (Barbier 2004). These endpoints were included in the Pediatric Investigation Plan and Pediatric Study Plan and agreed to by Paediatric Committee and FDA, respectively.

As the efficacy and safety of dupilumab for the treatment of AD has not yet been established in this age group, a placebo control is a scientifically essential element of the study design to enable adequate assessment and interpretation of the treatment effect and safety profile. It is particularly relevant for pediatric patients, in whom spontaneous remission of AD over time has been described. Several features of the protocol are intended to mitigate any potential adverse effects in patients randomized to the placebo group:

- Mandatory requirement for use of concomitant topical corticosteroids
  - Starting on day -14, all patients will initiate a standardized TCS treatment regimen with a medium-potency TCS that may be adjusted based on clinical response. Topical corticosteroids represent the mainstay of pharmacologic treatment of AD and have been shown to have some benefit even in a patient population selected for their inadequate response to TCS.
- Availability of rescue treatment
  - Patients who experience AD exacerbations or intolerable symptoms may receive rescue treatment with a range of treatments available to all patients with AD (except for very-high-potency TCS, as their use is not recommended in patients <12 years of age): high-potency TCS, systemic corticosteroids, and nonsteroidal immunosuppressive drugs
- Open-Label Extension Study (OLE)
  - 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). Additional details concerning eligibility for the OLE can be found in Section 7.9.

As described in Section 5.3.1, an Independent Data Monitoring Committee (IDMC), will monitor patient safety by conducting formal reviews of accumulated safety data on a program-wide level.

3.2.2. Rationale for Dose Selection

The dose justification for pediatric patients aged ≥6 years to <12 years is based on the observed efficacy and safety in the dose ranging study in adult AD patients (R668-AD-1021), the observed efficacy and safety in the phase 3 monotherapy studies in adult AD patients (R668-AD-1334 and R668-AD-1416), the observed PK data, efficacy and safety results in a pediatric AD study of patients ≥6 to <18 years old (R668-AD-1412). The selection of these dosing regimens is further supported by population PK modeling.

The adult dose-ranging study evaluated dupilumab dose regimens of 300 mg QW, 300 mg Q2W, 300 mg once every 4 weeks (Q4W), 200 mg Q2W, and 100 mg Q4W versus placebo, administered for 16 weeks. All 5 dose regimens were efficacious. The mean pharmacodynamic

(PD) effect/efficacy of dupilumab (represented by change in EASI, IGA, and Pruritus Numerical Rating Scale [NRS] scores) at week 16 generally aligned in the same rank order as the total monthly dose and the mean concentrations of functional dupilumab at week 16. Thus, the 300 mg QW regimen was consistently the most efficacious dose regimen in this study across multiple endpoints, followed closely by the 300 mg Q2W dose regimen. Differences in the efficacy and safety outcomes between the 300 mg QW and 300 mg Q2W were relatively small. The 200 mg Q2W and 300 mg Q4W doses also showed good efficacy responses but were numerically inferior to the 300 mg Q2W and 300 mg QW regimens for the majority of efficacy endpoints. The efficacy of the 100 mg Q4W regimen (100 mg total monthly dose) appeared to be sub-optimal

Study R668-AD-1412 was a phase 2a, multicenter, open-label, ascending-dose, sequential-cohort study investigating the safety, tolerability, PK, immunogenicity, and efficacy of single-dose and repeat-doses of dupilumab administered SC in pediatric patients with moderate to severe AD (for adolescents ≥12 to <18 years old) or severe AD (for school-going children ≥6 to <12 years old) that was not adequately controlled with topical treatments. The 2 assessed dose regimens at 2 mg/kg and 4 mg/kg correspond to the weight normalized dose in adults at 150 mg and 300 mg, respectively. Dupilumab administered as single and repeated weekly doses of 2 mg/kg and 4 mg/kg for 4 weeks was generally well tolerated with an acceptable safety profile in both pediatric age groups included in that study. There was a higher incidence of TEAEs following single and repeated weekly administration of 4 mg/kg compared to 2 mg/kg in both age-groups. This was driven by a higher incidence of nasopharyngitis and skin infections in the 4 mg/kg dose arm versus the 2 mg/kg dose arm. However, most of the adverse events (AEs) were mild in intensity, transient in nature, and not related to study drug. The most common AE reported after both single doses and repeated weekly doses was nasopharyngitis.

In children aged ≥6 to <12 years, dupilumab administered as a single dose of either 2 mg/kg or 4 mg/kg, in the study R668-AD-1412, induced a significant and rapid reduction of disease activity in patients at week 2 (37% and 33% reduction in EASI score from baseline for 2 mg/kg and 4 mg/kg doses, respectively). Repeated weekly doses of dupilumab led to a further improvement in disease severity in patients in both dose groups (76% and 63% reduction in EASI score from baseline for 2 mg/kg and 4 mg/kg doses, respectively, at week 12). There did not appear to be a clear dose response, as the 2 dose groups showed similar efficacy on the various endpoints evaluated during the study. The small sample size may have limited the precision of this study, but these data are consistent with saturation of the IL-4 receptor after 4 weekly doses of either 2 mg/kg or 4 mg/kg.

The collective clinical data on the exposure versus efficacy and safety in the adults and pediatric population as observed to date supports a similar exposure-response relationship for efficacy and safety between the adult and pediatric populations down to 6 years of age and justify the approach of selecting dose regimens for this study based on the criteria of matching adult exposure.

To account for body size difference in the pediatric population and taking into account the observed large therapeutic indices of dupilumab, a tiered fixed dosing regimen was chosen over weight based (mg/kg) dosing for ongoing development. This approach reduces the risk of dosing errors that can occur with weight-based dosing, as well as allowing for dosing convenience by simplifying administration using a prefilled syringe/device.

A population PK model was used to describe the exposure of dupilumab in the population identified in this protocol. This model, initially based on drug concentration data from studies conducted in adults, was further informed by the exposure data of the study(s) conducted in pediatric patients (R668-AD-1412). The PK modeling for dupilumab has shown weight to be the most important covariate influencing exposure, with exposure being inversely correlated with body weight. Outside of the effect of body weight on PK, the existing data do not suggest an age-related effect on exposure.

Data gathered from NHANES (n=1269) show that median weight in the children aged 6 to11 years old is = 32 kg (Q1=25, Q3=42). Simulations from the PK model suggest that the adult dose regimens (300 mg QW and 300 mg Q2W) may lead to systemic exposure in these children that is greater than the maximum exposure observed in adults. Hence, these doses are not supported by the safety data obtained in adults and will not be studied in children.

For the 200 mg Q2W regimen in children aged ≥6 to <12 years old who weigh >30 kg, the simulated exposure substantially overlaps with the efficacious exposure in adults from studies R668-AD-1021, R668-AD-1334, R668-AD-1416 and R668-AD-1224 (300 mg Q2W and QW). In addition, in study DRI12544 (a phase 2b study in patients with moderate to severe uncontrolled asthma) (300 mg Q2W) a strongly positive benefit-risk was identified. Hence, the proposed 200 mg Q2W dosing regimen for children aged ≥6 to <12 years old weighing >30 kg is expected to have a significant clinical benefit with an appropriate safety profile, under the assumption that PK/PD relationship is similar in pediatrics and adult patients.

A dose regimen of 100 mg Q2W SC has not been evaluated to date in the dupilumab program. However, based on simulations from the PK model, the use of 100 mg Q2W is expected to provide mean exposure in children ≥6 to <12 years old who weigh <30 kg that is similar to that for 200 mg Q2W in children >30 kg, thereby supporting the use of this regimen in the lower weight group. Moreover, the 100 mg dose can be delivered using a lower volume of injection. Since volume of injection has been shown to be an important factor impacting the tolerability of SC injections (Heise 2014), the smaller injection volume associated with the100 mg injection may offer some advantage in this population.

The 300 mg Q4W regimen was chosen to be included as a dosing option with less frequent injections. With this regimen, in children ≥6 to <12 years old and weight >30 kg, simulated dupilumab exposure at steady-state, specifically C_{max}, C_{trough}, and weekly area under the curve (AUC) were lower than for the 200 mg Q2W. Study R668-AD-1021 demonstrated that efficacy for the 300 mg Q4W regimen was statistically superior to placebo in adults. Pharmacokinetic simulations have shown that in children with weight >30 kg, the steady-state exposure was higher for the 300 mg Q4W regimen than in adults with the same regimen, but is not expected to exceed that for adults receiving 300 mg Q2W.

In children with weight <30 kg, simulated mean weekly AUC at steady-state for the 300 mg Q4W regimen was similar to that in adults receiving 300 mg Q2W, while C_{max} was higher and C_{trough} was lower. Data gathered from this dose regimen will enable PK/PD modeling to better characterize the exposure-response relationship in pediatric patients. A less frequent dosing regimen is expected to enhance compliance, especially in a pediatric population.

The administration of the loading dose of dupilumab will allow systemic concentrations to reach effective concentrations faster, and potentially reduce the time to onset of clinical effect.

3.2.3. Safety Considerations

R668-AD-1412 was a phase 2 study to evaluate the PK and safety of dupilumab in patients aged ≥6 years to <18 years, with moderate-to-severe AD. Dupilumab administered as single and repeated weekly doses of 2 mg/kg and 4 mg/kg for 4 weeks was generally well tolerated with an acceptable safety profile in both pediatric age groups (12 to 17 years old and 6 to 11 years old) included in this study. There was a higher incidence of TEAEs after administration of a single dose of 4 mg/kg as compared to 2mg/kg dose in both age-groups. Similarly, there was a higher incidence of TEAEs after administration of repeated weekly doses of 4 mg/kg as compared to repeated weekly doses of 2 mg/kg in both age-groups. This was driven by a higher incidence of nasopharyngitis and skin infections in the 4 mg/kg as compared to 2 mg/kg dose arm. The most common AE reported after both single doses and repeated weekly doses was nasopharyngitis.

In children 12 to <18 years old, there were 2 SAEs reported in each dose group (in the 2 mg/kg group, the SAEs reported were palpitations and infected AD; in the 4 mg/kg group, the SAEs reported were staphylococcal skin infection and infected AD). In children 6 to 11 years old, 2 patients in the 4 mg/kg dose group had serious TEAEs (2 events of exacerbation of AD, septic arthritis of the hip joint, and infected AD). None of these serious TEAEs was assessed by the investigators as drug-related. The events of infected AD and staphylococcal skin infections occurred in patients who were not being treated with dupilumab at time of onset of the SAE (patients were either in follow-up period of part A or in follow-up period of part B). It is well known that a very high proportion of patients with AD have skin colonization (Ong 2010) and patients with AD are prone to developing skin infections. Dupilumab, by treating AD, should lead to a reduction in skin infections. This is supported by data from phase 3 trials in adults with AD in which the incidence of serious and severe infections was numerically higher in the placebo group as compared to dupilumab (0.5% to 1% dupilumab and 2% to 3% placebo).

Positive anti-drug antibody (ADA) was observed in 50 patients (64.9 %) at any time, 31 of which (40.3% out of total) were categorized as persistent treatment-emergent ADA. The rate of occurrence of persistent ADA were similar across cohorts with a trend of higher rates in the adolescents compared with school-going children. Six patients (12.0%) had high titers (>10,000), 4 from the 2 mg/kg groups and 2 from 4 mg/kg groups. Within each age group, there also seemed to be a trend for higher incidence of persistent ADA in lower dose cohorts as compared to higher dose cohorts. Dupilumab concentrations in patients with high titers were markedly reduced compared to those with a negative response, or low or moderate titers. These patients had an inferior clinical response to the study drug as compared to the overall study population. The high titer ADAs were not associated with any systemic symptoms of hypersensitivity in these patients, although one of these patients did experience an injection site reaction, which was mild in intensity.

Standard safety monitoring used in previous trials with dupilumab is planned to be conducted during this study. An internal safety monitoring team will be reviewing blinded data at regular intervals during the study to monitor the safety of patients. An Independent Data Monitoring Committee (IDMC) overseeing the entire dupilumab clinical development will be in place for the duration of the study to monitor the safety of the patients and to provide the sponsor with appropriate recommendations in due time to ensure the safety of the patients.

Additional information can be found in the Investigator's Brochure.

3.2.4. Risk/Benefits of Participating in the Study

3.2.4.1. Benefits

The efficacy and safety of dupilumab in adults was evaluated in 4 randomized, double-blind, placebo-controlled studies and 1 dose-ranging study in patients with moderate-to-severe atopic dermatitis. In all studies, dupilumab treatment consistently reduced both the extent and severity of lesions as well as the severity of pruritus.

The first clinical study of dupilumab in pediatric patients aged 6 years to <18 years old has been completed (R668-AD-1412). Dupilumab administered as single and repeated weekly doses provided significant clinical benefit to pediatric patients in both age groups (6 years to 11 years and 12 to <18 years) consistent with that observed in adults.

3.2.4.2. Risks

Of the adverse drug reactions identified in the dupilumab adult AD clinical program, injection site reactions were very common (≥10%). Common adverse reactions (≥1% and <10%) included conjunctivitis, allergic conjunctivitis, eye pruritus, blepharitis, oral herpes, eosinophilia, and headache.

Serum sickness and serum sickness-like reactions occurred very rarely (<0.01%) (Dupixent [SmPC], 2017).

In the pediatric trial, the safety profile was consistent with that reported in adults. There were no new safety signals detected with dupilumab in the pediatric population.

One serious case each of serum sickness and serum sickness-like reaction (both associated with high ADA titers) were reported in adult AD studies. Additionally, there has been 1 report of anaphylaxis considered related to study drug by the investigator in an asthma study (Dupilumab [Investigator Brochure, 2017]. No AEs of systemic hypersensitivity were reported in the pediatric study. In study R668-AD-1652, patients will be monitored at the trial site for 2 hours post-dose for the first 3 visits at which study drug is administered to facilitate detection and treatment of any immediate hypersensitivity reactions to the study drug.

A higher incidence of conjunctivitis-related events has been observed in dupilumab-treated subjects as compared to placebo in the AD studies. A predominant number of these cases were non-serious, mild to moderate in severity, reported recovered/recovering during the active study periods, and infrequently led to study drug discontinuation. Neither a consistent dose response nor a consistent time to onset of these events have been observed.

Similarly, a higher incidence of injection site reactions has been observed in the dupilumab treated subjects, consistent with the subcutaneous injection of a protein biologic. There have been no serious events of ISR, and these events have infrequently led to study drug discontinuation (Dupilumab [Investigator Brochure, 2017]).

3.2.4.3. Risk/Benefit Conclusion

The safety data available to date, in conjunction with the risk monitoring and mitigation strategies in the study protocol, and the clinical benefit of dupilumab demonstrated in multiple AD studies, support a favorable benefit-risk profile for dupilumab.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc.), disease characteristics including medical history (including asthma), and medication history for each patient.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

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

4.2.2. Secondary Endpoints

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

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 Body Surface Area (BSA) affected by AD
- Percent change from baseline to week 16 in Scoring Atopic Dermatitis (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 at 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 Children's Dermatology Life Quality Index (CDLQI)
- Change from baseline to week 16 in Patient Oriented Eczema Measure (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- and 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

4.2.3. Other Endpoints and Assessments

Other endpoints and assessments, as applicable, will be specified in the statistical analysis plan (SAP).

4.3. Pharmacokinetic Variables

Concentration of functional dupilumab in serum at each time point will be considered to be trough values ($C_{trough.timepoint}$).

4.4. Anti-Drug Antibody Variables

Anti-drug (dupilumab) antibody variables include status (positive or negative) and titer as follows:

- Total number of patients negative in ADA assay at all time
- Total number of patients positive in ADA assay at any time
- Total number of patients with preexisting immunoreactivity – defined as either an ADA positive response in the assay at baseline with all post-baseline ADA results negative, or a positive response at baseline with all post-baseline ADA titer <4-fold over baseline titer level

- Total number of patients with treatment-emergent ADA response in ADA assay – 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 into the following categories:
  - Persistent ADA response – a treatment-emergent ADA positive response with 2 or more consecutive positives in the ADA assay separated by greater than a 12-week period, with no ADA negative samples in between
  - Transient ADA response – a treatment-emergent ADA positive response that is not considered persistent or indeterminate
  - Indeterminate ADA response – a treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay
- Total number of patients with a treatment-boosted response – defined as a positive response in the ADA assay post first dose that is ≥4-fold over baseline titer levels when baseline results are positive
- Titer value category
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

Anti-drug antibody positive samples will be further characterized for the presence of neutralizing antibody (NAb) response:

- Total number of patients positive in the NAb assay at the time points analyzed.

5. STUDY DESIGN

5.1. Study Description and Duration

This is a randomized, double-blind, placebo-controlled, parallel-group study in which study treatments (dupilumab/placebo) will be administered concomitantly with TCS. Approximately330 study patients are planned to be enrolled in the study.

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)

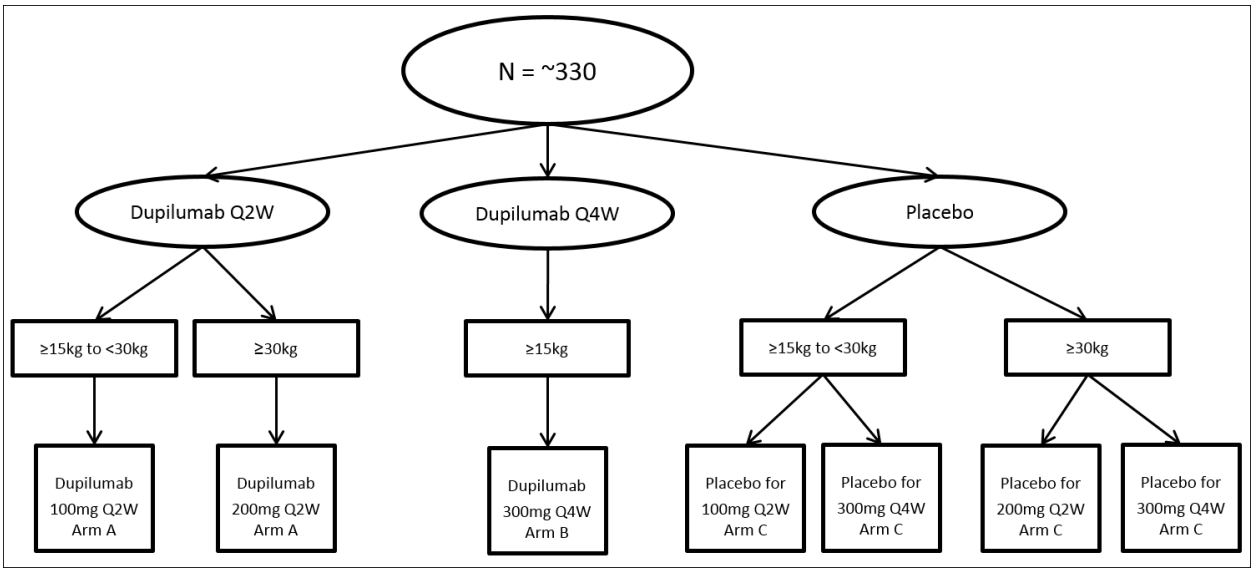
After the parents or legal guardians provide informed consent and patients provide assent, the patients will be assessed for study eligibility at the screening visit. During the screening period, systemic treatments for AD will be washed out, as applicable, according to the eligibility requirements (provided in Section 6.2.1 and Section 6.2.2). 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 in Section 7.2. Patients may be rescreened, unless the reason for the screen failure is related to failing the disease severity inclusion criteria. Patients should 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) as follows:

- dupilumab Q2W treatment group:
  - 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: 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: 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: Study Design

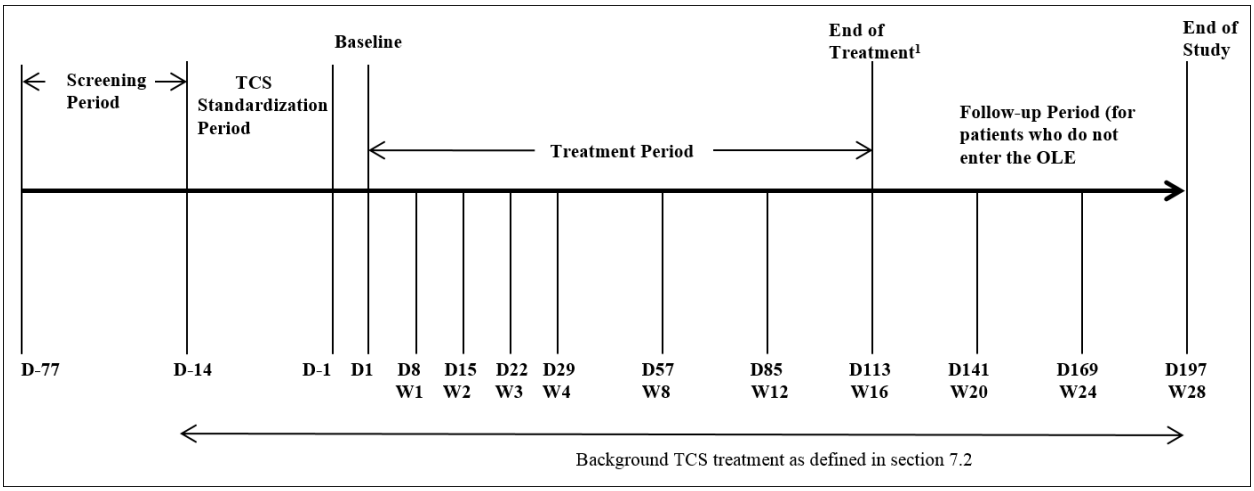


Arm A consists of patients receiving Q2W treatment, either 100 mg for patients weighing <30 kg or 200 mg for patients weighing ≥30 kg. Arm B consists of patients receiving Q4W treatment , 300 mg regardless of weight. Arm C consists of patients receiving placebo treatment Q2W and Q4W and matching the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

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 Table 1. 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 Table 2.

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.

5.1.1. End of Study Definition

The end of study definition is defined as the last visit for the last patient.

5.2. Planned Interim Analysis

No interim analysis with alpha spending is planned for this study. An unblinded first-step analysis **may** be performed once all patients in the study have completed the 16-week treatment period as specified in the protocol (week 16 visit or earlier for those patients who are withdrawn prematurely from the study). If performed, this first-step analysis will be considered the final analysis for the primary and secondary efficacy endpoints. A description of the statistical methods to be employed and blinding implications are in Section 10.5.2.4.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An IDMC, composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 330 patients are planned to be enrolled at multiple sites in the US and EU into 3 groups (at 1:1:1 ratio): dupilumab Q2W treatment group (100 mg Q2W or 200 mg Q2W), dupilumab Q4W treatment group (300 mg Q4W), or placebo group (Q2W or Q4W).

6.2. Study Population

The study population includes pediatric patients (aged ≥6 to <12 years at the time of screening) who have severe AD that cannot be adequately controlled with topical AD medications.

6.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female ≥6 to <12 years of age at time of screening visit
2. Diagnosis of AD according to the American Academy of Dermatology consensus criteria (Eichenfield 2003) at screening visit
3. Chronic AD diagnosed at least 1 year prior to the screening visit
4. IGA = 4 at screening and baseline visits
5. EASI ≥21 at the screening and baseline visits
6. BSA ≥15% at screening and baseline visits
7. Baseline worst itch score weekly average score for maximum itch intensity ≥4

   NOTE: Baseline worst itch average score for maximum itch intensity will be determined based on the average of daily worst itch scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. A complete daily score consists of answers to both questions.

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

   For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 77-day maximum duration for screening plus TCS standardization.

8. With documented recent history (within 6 months before the baseline visit) of inadequate response to topical AD medication(s). For more information, see the note below.

   NOTE:

   - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to high potency (±TCI as appropriate), applied for at least 28 days
   - Patients with documented systemic treatment for AD in the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with dupilumab after appropriate washout.
   - Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician. If documentation is inadequate, potential patients may be offered a course of treatment with a daily regimen of TCS of medium potency, applied for at least 28 days during the screening period (including the 2 weeks TCS standardization period). Patients who demonstrate inadequate response during this period, as defined above, will be eligible for inclusion in the study, as long as they meet other eligibility criteria.

9. At least 11 (of a total of 14) applications of a stable dose of topical emollient (moisturizer) twice daily during the 7 consecutive days immediately before the baseline visit
10. Willing and able to comply with all clinic visits and study-related procedures
11. Patient, either alone or with help of parents/legal guardians, as appropriate, must be able to understand and complete study-related questionnaires
12. Parent or legal guardian must provide signed informed consent. Patients must also provide separate informed assent to enroll in the study, and sign and date either a separate informed assent form (IAF) or the informed consent form (ICF) signed by the parent/legal guardian (as appropriate based on local regulations and requirements)

6.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Participation in a prior dupilumab clinical study
2. 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

3. Treatment with a topical investigational drug within 2 weeks prior to the baseline visit
4. Treatment with crisabarole within 2 weeks prior to the baseline visit

5. 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.

6. Treatment with a TCI within 2 weeks prior to the baseline visit
7. 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
8. 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
9. 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.

10. Planned or anticipated use of any prohibited medications and procedures during study treatment
11. Body weight <15 kg at baseline

12. 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)
13. Regular use (more than 2 visits per week) of a tanning booth/parlor within 8 weeks of the baseline visit
14. 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
15. 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 immune-compromised status, as judged by the investigator
16. 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.
17. Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit
18. 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.
19. 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
20. 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

21. Presence of any 1 or more of the following abnormalities in laboratory test results at screening:
    - Platelets $\leq 100 \times 10^3/\mu L$
    - Neutrophils $< 1.5 \times 10^3/\mu L$
    - 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.
22. 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.
23. History of malignancy before the baseline visit
24. 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
25. 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).
26. 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.).
27. Planned major surgical procedure during the patient's participation in this study
28. Patient or his/her immediate family is a member of the dupilumab investigational team
29. Patient is female who is pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study
30. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

31. 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 subject.

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.

6.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion. The parent/caregiver has the right to withdraw permission to have the patient participate in the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, AE, treatment failure, protocol violation, cure, and for administrative, or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who withdraw prematurely from the study will be asked to complete study assessments per Section 8.1.

6.4. Replacement of Patients

Patients prematurely discontinued from the study or study treatment will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Dupilumab 175 mg/mL: Each 1.14 mL single-use, prefilled glass syringe with snap-off cap delivers 200 mg of study drug (1.14 mL of a 175 mg/mL solution).

Dupilumab 150 mg/mL: Each 2.25 mL single-use, prefilled glass syringe with snap-off cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)

Dupilumab 150 mg/ml: Each 0.7 mL single-use, prefilled glass syringe with snap-off cap delivers 100 mg study drug (0.7 mL of a 150 mg/mL solution).

Placebo matching dupilumab is prepared in the same formulation without the addition of protein (ie, active substance, anti-IL-4Rα monoclonal antibody). Three matching placebo formulations will be used:

1. 2 mL placebo matching 300 mg dupilumab formulation
2. 1.14 mL placebo matching 200 mg dupilumab formulation
3. 0.7 mL placebo matching 100 mg dupilumab formulation

Patients will be randomized to receive 1 of the treatment regimens described in Section 5.1.

Study drug will be administered per the schedule described in Section 8.1.

Subcutaneous injection sites of the study drug should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. To allow for adequate assessment of possible injection site reactions, study drug should be administered only into areas of normal-looking skin (for patients with 100% BSA involvement, the injection should be administered into as near normal looking skin as possible). Instructions for recording and reporting injection site reactions will be provided in the study reference manual.

Parents/caregivers will have the option to administer study drug outside the study site during weeks in which no in-clinic visit is scheduled (for patients receiving Q2W treatment). The study staff will train the parent/caregiver on preparation and administration of study drug on day 1 and will administer the first of the 2 injections required for the loading dose. The parent/caregiver will administer the second injection required for the loading dose under the supervision of the clinic staff. The parent/caregiver will administer study drug under the supervision of the clinic staff at visits 5 and 7 (weeks 2 and 4, respectively) and at other in-clinic visits. Patients will be monitored at the study site for a minimum of 2 hours after the first 3 doses of study drug (visits 3 [day 1], 5 [week 2], and 7 [week 4] for patients receiving Q2W treatment and visits 3 [day 1], 7 [week 4], and 11 [week 8] for patients receiving Q4W treatment); vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature) and AE assessments will be done at 30 minutes (±10 minutes) post dose and then at 2 hours (±15 minutes). The parent/caregiver will administer study drug outside of the clinic during weeks in which no clinic visit is scheduled.

Parents (or caregivers) who prefer to have the clinic staff administer study drug may choose to have injections administered in the clinic.

7.2. Background Treatment

All patients should apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization. After randomization, patients are required to continue to apply moisturizers throughout the study (all 28 weeks where applicable). However, to allow adequate assessment of skin dryness, moisturizers should not be applied for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers (eg, ceramide containing products like epiceram®) or moisturizers containing additives (ceramide, hyaluronic acid, urea, filaggrin degradation products) during the screening period or during the study. Patients may continue using stable doses of such moisturizers if initiated before the screening visit.

Starting on day -14, all patients are required to initiate treatment with TCS using a standardized regimen according to the following guidelines:

- Apply medium-potency TCS once daily to areas with active lesions. Based on investigator discretion, low-potency TCS may be used once daily on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) or for areas where continued treatment with medium-potency TCS is considered unsafe.
- Once the patient achieves an IGA score of 2 or less, decrease the frequency of use of medium-potency TCS to 3 times per week, and then stop once lesions are clear (IGA 0). Patients should be instructed to use TCS only on active lesions, and to stop use of TCS if lesions clear completely in between clinic visits.
- If lesions return, reinstitute treatment with medium-potency TCS, with the same step-down approach described above upon lesion resolution.
- In case there are signs of local (eg, impending skin atrophy), or systemic TCS toxicity with medium-potency steroids, patients should be switched to low-potency steroids.
- For lesions persisting or worsening under daily treatment with medium-potency TCS, patients may be treated (rescued) with high-potency TCS (super-potent/ very-high-potency steroids are not allowed even for rescue), unless higher potency TCS are considered unsafe (a potent TCS should normally be restricted to use on non-delicate skin sites [excluding face, flexures, groin], and should not be used for a prolonged period in order to prevent the development of cutaneous atrophy and adrenal axis suppression. Low-potency steroids should normally be used for delicate skin sites (face, flexures, groin) during these flares.
- A list of steroids that can be used during the study will be provided to the investigators as part of the study manual. The use of very-high potency or superpotent TCS is prohibited during the study, as their use is not recommended in patients under 12 years of age. If patients have tolerance issues with any of these steroids, and/or to the excipients in a particular formulation (eg, hypersensitivity), or if they are not commercially available, they may substitute with products of the same potency from the list provided in the study manual. It is recommended that patients use triamcinolone acetonide 0.1% cream, fluocinolone acetonide 0.025% cream, or clobetasone butyrate 0.05% for medium potency, and hydrocortisone acetate 1%

cream for low potency. If rescue with TCS is needed, it is recommended that patients use mometasone furoate 0.1% ointment as high-potency steroid. If patients have tolerance issues with any of these steroids or if they are not commercially available, they may substitute with products of the same potency from the list provided in the study reference manual.

- A 60-minute interval between the application of emollients and TCS is recommended, wherever applicable.
- Patients will return TCS tubes at each clinic visit through week 16, and these tubes will be weighed by the site staff to determine the actual amount of TCS used.

7.3. Rescue Treatment

Rescue treatment for AD may be provided to patients during the study. Investigators will be required to perform an IGA assessment prior to starting rescue treatment and initiate rescue treatment only in patients who either have an IGA score = 4, or have intolerable symptoms. If possible, investigators are encouraged to consider rescue initially with topical treatment (eg, 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. The use of very-high-potency or superpotent TCS is prohibited in this study, even as rescue treatment, as their use is not recommended in patients under 12 years of age. Very-high-potency topical corticosteroids include:

- Betamethasone dipropionate augmented 0.05% ointment
- Clobetasol propionate 0.05% solution, foam, cream or ointment
- Diflorasone diacetate 0.05% ointment
- Halobetasol propionate 0.05% cream or ointment

Patients who receive systemic corticosteroids or systemic non-steroidal immunosuppressive drugs (eg, 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 (eg, 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.

7.4. Dose Modification and Study Drug Discontinuation Rules

7.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.

7.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently discontinued in the event of:

- Anaphylactic reaction or other severe systemic reaction to dupilumab
- Diagnosis of a malignancy during study
- Evidence of pregnancy
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities that are deemed to be related to dupilumab:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values greater than 3 × ULN with total bilirubin >2 × ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks)
- Treatment with any prohibited concomitant medication or procedure (Section 7.8.1). NOTE: The use of TCI is prohibited during the 2-week TCS standardization period leading up the baseline visit, and the treatment and follow-up periods. The use of very-high-potency or superpotent TCS is not allowed throughout the study (as their use is not recommended in patients under 12 years of age). However, high-potency TCS can be used as rescue. In this situation, the study drug will be continued.

7.4.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing may be temporarily discontinued in the event of:

- Clinically important laboratory abnormalities, such as:
  - ALT or AST 3 × ULN but ≤5 × ULN
  - Neutrophil count $<1.5 \times 10^3/\mu L$ but $>0.5 \times 10^3/\mu L$
  - Platelet count $\leq 100 \times 10^3/\mu L$ but $>50 \times 10^3/\mu L$
  - CPK >5 × ULN
  - Serum creatinine >1.5 × ULN
  - Eosinophils >5000/µL

- Severe laboratory abnormalities (as noted in Section 7.4.2.1) where a causal relationship to dupilumab can be reasonably excluded (ie, an alternative cause is evident). In these cases, study treatment will be discontinued while the clinical circumstances are being assessed but it may be resumed when the laboratory parameters normalize sufficiently. A decision to resume treatment will be made jointly by the investigator and medical monitor.
- Other intercurrent illnesses or major surgery
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents, or requires oral treatment with such agents for longer than 2 weeks

After the condition leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. A decision to discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. Note that dosing may NOT be resumed if patient met conditions for permanently discontinuing study drug described in Section 7.3. The investigator may suspend study treatment at any time, even without consultation with the medical monitor, if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

7.5. Management of Acute Reactions

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

7.6. Method of Treatment Assignment

Approximately 330 patients will be randomized, stratified by weight group (<30 kg or ≥30 kg) and region (North America, Europe), to 1 of the treatment groups described in Section 5.1 according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

7.6.1. Blinding

With the exception of the IDMC members and the provisions in Section 7.6.2, this study will remain blinded to all individuals until the prespecified unblinding to conduct the primary analyses.

Blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody and drug concentration results will not be communicated to the sites, and the sponsor's operational team will not have access to results associated with patient identification until after the final database lock.

7.6.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency, an SAE that is unexpected and for which a causal relationship to the study drug cannot be ruled out, or any other significant medical event (eg, pregnancy).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patient will be unblinded.
  - The IVRS/IWRS will provide the treatment assignment to the investigator.
  - The investigator will notify Regeneron and/or designee immediately that the patient has been unblinded.

7.7. Treatment Logistics and Accountability

7.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used in labeling blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site [redacted]; storage instructions will be provided in the pharmacy manual.

7.7.2. Supply and Disposition of Treatments

Study drug will be shipped [redacted] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

7.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication.

- dispensed to each patient,
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.7.4. Treatment Compliance

All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

7.8. Concomitant Medications and Procedures

Any treatment administered from the time of the first dose of study drug to the final study visit will be considered concomitant medication. This includes medications that were started before the first dose of study drug and are ongoing during the study.

7.8.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited during the study:

- Treatment with a live (attenuated) vaccine; below is a list of examples of such vaccines; refer to study manual for a current, comprehensive list of prohibited vaccines

  Chickenpox (Varicella)
  FluMist-Influenza
  Intranasal influenza
  Measles (Rubeola)
  Measles-mumps-rubella combination
  Measles-mumps-rubella-varicella combination
  Mumps
  Oral polio (Sabin)
  Oral typhoid
  Rubella
  Smallpox (Vaccinia)
  Yellow fever
  Bacillus Calmette-Guerin
  Rotavirus
  Varicella Zoster (shingles)

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating biologics
- Treatment with systemic nonsteroid immunosuppressant (may be used as rescue, see Section 7.3 for details)
- Treatment with systemic corticosteroids (may be used as rescue, see Section 7.3 for details)
- 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 TCS, (high-potency TCS may be used as rescue, see Section 7.3 for details). The use of very-high-potency or superpotent TCS (a fluticasone or hydrocortisone comparator strength) is prohibited during the study (as their use is not recommended in patients < 12 years of age).
- 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)

7.8.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 7.8.1, treatment with concomitant medications is permitted during the study. This includes basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications for any duration.

Medications used to treat chronic disease such as diabetes, hypertension, and asthma are also permitted. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

7.9. Continuation of Dupilumab Treatment in an Open-Label Extension Study

All patients will be offered the opportunity to screen for entry into OLE at end of treatment period (week 16). Patients who decline to enroll in the OLE study, or those who fail eligibility criteria for OLE, will have a 12-week follow-up period.

8. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

8.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 (screening, baseline, and treatment period) and in Table 2 (follow-up period, unscheduled visits, and early termination).

Table 1: Schedule of Events (Screening, TCS Standardization, Baseline, and Treatment Period)

	SCN	TCS standardization	Treatment Period																
			BL																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	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	W 2	W3	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 treatment)[4]			X		X		X												

	SCN	TCS standardization	Treatment Period																
			BL																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	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	W 2	W3	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
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 receiving Q2W treatment)											X				X				X

	SCN	TCS standardization	Treatment Period																
			BL																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	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	W 2	W3	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
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 impression of disease[10,11]	X		X		X		X				X				X				X

	SCN	TCS standardization	Treatment Period																
			BL																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	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	W 2	W3	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
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
Vital signs[5]	X	X	X	X	X	X	X				X				X				X
Physical examination	X																		X

	SCN	TCS standardization	Treatment Period																
			BL																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	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	W 2	W3	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
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																

	SCN	TCS standardization	Treatment Period																
			BL																**EOT**[17]
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	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	W 2	W3	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

SCN = screening; BL = baseline; Ser = serum; Ur = urine; WOCBP = women of childbearing potential; TB = tuberculosis

Note: The length of the screening period is not fixed, but the duration for screening and TCS standardization 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
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

8.1.1. Footnotes for Schedule of Events Table

8.1.1.1. 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 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 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 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.

8.1.1.2. 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 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.

8.1.2. Early Termination Visit

Patients who are withdrawn from the study will be asked to return to the clinic for early termination assessments as per Table 2.

8.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. The specific assessments that will be performed at the unscheduled visit will depend on the reason for the unscheduled visit.

8.2. Study Procedures

Assessments/procedures at the clinic visit should be performed in the following order:

1. Patient Reported Outcomes (completed by patients with help of parents/caregiver if required). Patient assessment of injection pain will be performed after administration of study drug.
2. Investigator assessments (performed only by adequately trained and qualified investigators or sub-investigators; it is recommended that the same investigator or sub-investigator perform all the evaluations for a given patient throughout the entire study period)
3. Safety and laboratory assessments
4. Administration of study drug

8.2.1. Procedures Performed only at the Screening/Baseline Visit

These procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: medical history and demographics. The following tests will be performed at screening: HIV, HBsAg, HBsAb, HBcAb, hepatitis C antibody, and tuberculosis (will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards).

8.2.2. Efficacy Procedures

A variety of parameters will be collected during the study to assess efficacy/effectiveness of dupilumab, including measures of AD severity, use of concomitant treatment for AD, and patient-reported measures of AD symptoms and QOL.

Questionnaires and patient-reported assessments should be administered prior to obtaining investigator assessments, safety and laboratory assessments, and study drug administration. Please see study manual for instructions on the administration and use of all patient-reported instruments (including worst itch score, patient global impression of disease, patient global impression of change, CDLQI, POEM, PROMIS anxiety and depression score, Faces pain scale, and DFI).

8.2.2.1. Patient Assessment of Pruritus Using 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 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 Section 8.1). Both questions will be answered in the evening (it is recommended that the questions be answered and the responses provided in the diary in the 6:00 PM to 11:00 PM local time window). The daily worst itch score will be calculated as the worse of the scores for the 2 questions.

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.

This questionnaire measures concept(s), which are known only/best to the patient suffering from AD. As such the questionnaire is designed for self-report. Where possible the patient should read and complete the questionnaire alone. Where required, a caregiver (parent or other) can read the questions and response options aloud to the person with AD. However, it is important that the patient's selected responses to the questions are entered directly into the questionnaire. The caregiver must not influence or question the response given by the person with AD. This should be communicated to caregivers during the first visit. A field to indicate whether the question and response options were read out to the patient by caregiver has been added to the first page of the diary/questionnaire.

8.2.2.2. Patient Global Impression of Disease

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

In general, how itchy have you been during the last 7 days?

- Not itchy at all
- A little itchy
- Medium itchy
- Pretty itchy
- Very itchy

Patients will undergo this assessment at time points according to Section 8.1. This questionnaire measures concept(s), which are known only/best to the patient suffering from AD. As such the questionnaire is designed for self-report. Where possible the patient should read and complete the questionnaire alone. Where required, a caregiver (parent or other) can read the questions and response options aloud to the person with AD. However, it is important that the patient's selected response to the questions are entered directly into the questionnaire. The caregiver must not influence or question the response given by the person with AD. This should be communicated to caregivers during the first visit. A field to indicate whether the question and

response options were read out to the patient by caregiver has been added to the first page of the diary/questionnaire. This information will be transferred to the eCRF.

The assessment tool is provided in the study reference manual.

8.2.2.3. Patient Global Impression of Change

Patients will respond to the following question based on the 5-level scale as follows:

Since you started your study medication, how has your itching changed?

- Much better
- A little better
- The same
- A little worse
- Much worse

Patients will undergo this assessment at time points according to Section 8.1. This questionnaire measures concept(s), which are known only/best to the patient suffering from AD. As such the questionnaire is designed for self-report. Where possible the patient should read and complete the questionnaire alone. Where required, a caregiver (parent or other) can read the questions and response options aloud to the person with AD. However, it is important that the patient's selected response to the questions are entered directly into the questionnaire. The caregiver must not influence or question the response given by the person with AD. This should be communicated to caregivers during the first visit. A field to indicate whether the question and response options were read out to the patient by caregiver has been added to the first page of the diary/questionnaire. This information will be transferred to the eCRF.

The assessment tool is provided in the study reference manual.

8.2.2.4. Children's Dermatology Life Quality Index

The CDLQI is a validated questionnaire designed to measure the impact of skin disease on the QOL in children (Lewis-Jones 1995). The aim of the questionnaire is to measure how much a patient's skin problem has affected the patient over a recall period of the past week. To complete the questionnaire, patients need to provide responses to 10 questions (the questions focus on domains such as symptoms feelings associated with disease, the impact of the disease on leisure, school or holidays, personal relationships, sleep, and side effects of treatment for the skin disease. The instrument has a recall period of 7 days. Nine of the 10 questions are scored as follows:

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

Question 7 has an additional possible response (prevented school), which is assigned a score of 3.

The CDLQI for a patient is the sum of the score of each question with a maximum of 30 and a minimum of 0. The higher the score, the greater the impact is on the QOL. The CDLQI can also be expressed as a percentage of the maximum possible score of 30.

Patients will undergo this assessment at time points according to Section 8.1. This questionnaire measures concept(s), which are known only/best to the patient suffering from AD. As such the questionnaire is designed for self-report. Where possible the patient should read and complete the questionnaire alone. Where required, a caregiver (parent or other) can read the questions and response options aloud to the person with AD. However, it is important that the patient's selected response to the questions are entered directly into the questionnaire. The caregiver must not influence or question the response given by the person with AD. This should be communicated to caregivers during the first visit. A field to indicate whether the question and response options were read out to the patient by caregiver has been added to the first page of the diary/questionnaire. This information will be transferred to the eCRF.

The CDLQI is provided in the study reference manual.

8.2.2.5. Patient Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency of these disease symptoms during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.

The questionnaire will be administered at time points according to Section 8.1. This questionnaire asks the caregiver to report their perception of patient's AD symptoms. It is therefore completed by the caregiver. To ensure consistency in perception over longitudinal administration and to minimize respondent variability, it is important that the same caregiver complete the questionnaire at each time point. This should be communicated to caregivers during consent and prior to the first completion of the questionnaire. A field has been added to the first page of the diary/questionnaire to indicate who completed the questionnaire (mother/female guardian, father/male guardian, other caregiver). This information will be transcribed into the eCRF along with the questionnaire.

8.2.2.6. Dermatitis Family Index

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 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 assessment will be performed a time points according to Section 8.1. This questionnaire asks the caregiver to report the impact of having a child with AD on the QOL of the family. It is therefore completed by the caregiver. To ensure consistency in perception over longitudinal administration and to minimize respondent variability, it is important that the same caregiver complete the questionnaire at each time point. This should be communicated to caregivers during consent and prior to the first completion of the questionnaire. A field has been added to the first page of the diary/questionnaire to indicate who completed the questionnaire (mother/female guardian, father/male guardian, other caregiver). This information will be transcribed into the eCRF along with the questionnaire.

The DFI questionnaire is provided in study reference manual.

8.2.2.7. Faces Pain Scale – Revised

The Faces Pain Scale – Revised (FPS-R) is a self-report measure of pain intensity developed for children (Hicks 2001). 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 scale shows a close linear relationship with visual analog pain scales across the age range of 4 to 16 years. It is easy to administer and requires no equipment except for the photocopied faces. The instrument has well established psychometric properties and has been validated in school-going children.

The instrument will be used to assess injection site pain at the time points specified in Section 8.1. This instrument measures concept(s), which are known only/best to the person who is administered the injection. As such the instrument is designed for self-report. Where possible the patient should read the instructions and complete the instrument alone. Where required a caregiver (parent or other) can read the instructions aloud to the person with AD. However, it is important that the person with AD's selected response is entered directly into the instrument. The caregiver must not influence or question the response given by the person with AD. This should be communicated to caregivers during the first visit. A field to indicate whether the instructions were read out to the patient by caregiver has been added to the first page of the diary/questionnaire. This information will be transferred to the eCRF.

The assessment tools are provided in the study reference manual.

8.2.2.8. PROMIS Anxiety and Depression Scale

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).

Both of these assessments need to be completed at the time points specified in Section 8.1. This questionnaire asks the caregiver to report their perception of the patient's anxiety and depressive symptoms. It is therefore completed by the caregiver. To ensure consistency in perception over longitudinal administration and to minimize respondent variability, it is important that the same

caregiver complete the questionnaire at each time point. This should be communicated to caregivers during consent and prior to the first completion of the questionnaire. A field has been added to the first page of the diary/questionnaire to indicate who completed the questionnaire (mother/female guardian, father/male guardian, other caregiver). This information will be transcribed into the eCRF along with the questionnaire.

The PROMIS anxiety and depression instruments are provided in the study reference manual.

8.2.2.9. Investigator's Global Assessment

The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score will be assessed at time points according to Section 8.1.

The IGA is provided in the study reference manual and in Appendix 2.

8.2.2.10. Eczema Area and Severity Index

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 is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). The EASI will be collected at time points according to Section 8.1.

NOTE: Each of the body regions (head and neck, trunk, upper limbs, lower limbs) is assigned a proportion of the total body surface area. These proportions vary with age and are different in young children as compared to older children.

The EASI assessment tool is provided in the study reference manual.

8.2.2.11. Global Individual Signs Score

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria (Section 8.2.2.10). The Global Individual Signs Score (GISS) will be assessed at time points according to Section 8.1.

The GISS assessment tool is provided in the study reference manual.

8.2.2.12. SCORing Atopic Dermatitis

The SCORing Atopic Dermatitis (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 (European Task Force on Atopic Dermatitis 1993). There are 3 components to the assessment: A = extent or affected BSA, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see Section 8.2.2.13) 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 of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, and dryness) is assessed 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, 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: $A/5 + 7B/2 + C$ where the maximum is 103. Patients will undergo this assessment at time points according to Section 8.1.

The SCORAD assessment tool is provided in the study reference manual.

8.2.2.13. Body Surface Area Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body using the rule of nines (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. Patients will undergo this assessment at time points according to Section 8.1.

NOTE: The proportion assigned to different body regions is different in younger children as compared to older children (head and neck area is assigned a higher proportion in younger children as compared to older children).

The BSA assessment tool is provided in the study reference manual.

8.2.2.14. 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 Section 8.1.

The assessment tool is provided in the study reference manual.

8.2.2.15. 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 Section 8.1. This questionnaire asks the caregiver to report the impact of having a child with AD on their workdays. It is therefore completed by the caregiver. To ensure consistency in perception over longitudinal administration and to minimize respondent variability, it is important that the same caregiver complete the questionnaire at each time point. This should be communicated to caregivers during consent and prior to the first completion of the questionnaire. A field has been added to the first page of the diary/questionnaire to indicate who completed the questionnaire (mother/female guardian, father/male guardian, other caregiver). This information will be transcribed into the eCRF along with the questionnaire.

8.2.2.16. Atopic Dermatitis Area Photographs

At select study sites, photographs will be taken of a representative area of AD involvement (eg, the lesional area used for SCORAD assessments on day 1/baseline [predose]). Subsequent photographs of the same area will be taken at time points according to Section 8.1.

Instructions for taking the photographs are provided in the photography reference manual.

8.2.2.17. Topical Corticosteroids Accountability

At every in-clinic visit following the TCS standardization visit, the type, amount, frequency, and potency of TCS used will be recorded by site personnel. The amount of TCS used will be determined by weighing the tube at each visit through the end of the study.

In addition, patients will be asked to record TCS use daily, from day -14 until the end of the study, by providing the following information on a diary:

- Use of TCS (Yes/No)

8.2.3. Safety Procedures

8.2.3.1. Vital Signs

Vital signs (including sitting blood pressure, heart rate, respiration, and temperature) will be collected at 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 Section 8.1 for assessment time points.

8.2.3.2. Body Weight and Height

Body weight and height will be measured at time points according to Section 8.1.

8.2.3.3. Physical Examination

A thorough and complete physical examination will be performed at visits according to Section 8.1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

8.2.3.4. Electrocardiogram

Electrocardiograms (ECGs) should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Section 8.1. Heart rate will be recorded from the ventricular rate, and the PR, QRS, RR and QT intervals will be recorded. The ECG strips or reports will be retained with the source.

8.2.3.5. Laboratory Testing

Hematology, serum chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to Section 8.1. 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× 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 Section 8.1. 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).

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

8.2.3.6. Ophthalmological Examinations

Patients who have a history of certain eye disorders (conjunctivitis, blepharitis or keratitis) within the last 12 months will be referred to an ophthalmologist (preferably with expertise in treating pediatric patients or Cornea and External Eye Disease [‘front-of-the-eye’] subspecialty expert). Any baseline findings will be documented as part of the patient’s medical history and/or physical exam, as appropriate.

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.

8.2.4. Pharmacokinetic and Antibody Procedures

8.2.4.1. Drug Concentration Measurements and Samples

Serum samples for measuring functional dupilumab concentrations will be collected at time points listed in Section 8.1.

8.2.4.2. Anti-Drug Antibody Measurements and Samples

Serum samples for ADA assessment will be collected at time points listed in Section 8.1.

Long term follow-up of patients who are ADA positive at their last study visit (early termination or end of study) and who do not participate in the open-label extension study may be considered based on the overall clinical presentation at that time.

8.2.5. Biomarker Procedures

Thymus and activation-regulated chemokine and total serum IgE are markers of type 2/Th2 activity as downstream mediators in the IL-4/IL-13 signaling pathway (Wirnsberger 2006, Takeda 1997). These analytes may be assessed as measures of type 2/Th2 activity and PD effect of dupilumab. The results may be used for modeling dupilumab activity with drug levels in the comparison of dosing regimens. Thymus and activation-regulated chemokine levels have also been closely associated with AD disease activity and severity (Beck 2014), and will be evaluated as an exploratory marker of efficacy. These markers may also be assessed for their potential value in predicting treatment response.

Lactate dehydrogenase levels have also been shown to correlate with disease severity and activity in patients with AD (Mukai 1990).

Serum samples for measurements of biomarkers (including TARC, total IgE, immunoglobulin profiling, and LDH [which will be measured as part of the blood chemistry]) to study the PD activity of dupilumab in pediatric AD patients will be collected at time points according to Section 8.1.

[redacted]

[redacted]

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patient. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IECs/IRBs as appropriate, and to the investigators.

Any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected. Any worsening of or new onset of symptoms related to AD, which occur during the screening/washout period prior to study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the study drug to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IECs/IRB as appropriate.

9.3. Definitions

9.3.1. Adverse Event

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

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drug.

9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events. See Section 9.3.3 for more information on recording and reporting SAEs.

9.3.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), by telephone within 24 hours of identification, any pregnancy occurring in a female patient during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: Adverse events of special interest (AESI) must be reported within 24 hours of identification. Adverse events of special interest for this study include:

- 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)

Any patient who experiences an adverse event of special interest related to an eye disorder will be referred to an ophthalmologist. Futher evaluation of these AESIs will be performed including any additional tests, as per the discretion of the ophthalmologist.

Refer to the study reference manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manual for the procedures to be followed.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

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

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

- **Mild**: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity
- **Moderate**: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity
- **Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

9.5.2. Evaluation of Causality

Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

For a list of factors to consider in assessing the relationship of AEs to study drug, see Appendix 1.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

9.6. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

The following null hypothesis and alternative will be tested for each dupilumab treatment group:

H0: No treatment difference between dupilumab and placebo

H1: There is a treatment difference between dupilumab and placebo

Baseline weight group (<30 kg and ≥30 kg) and region (North America/Europe) will be the 2 stratification factors for patient randomization and will be accounted for in the statistical modeling for efficacy.

10.2. Justification of Sample Size

Based on the initial sample size of 240 patients (prior to this amendment), it is estimated that with 80 patients per group, at the 2-sided 5% significance level, the study will have:

- 97% power to detect a difference of 23% between dupilumab Q2W treatment and placebo treatment (both in combination with TCS) in the percentage of patients who achieve an IGA score 0 or 1 at week 16, assuming that the percentages are 28% and 5% for dupilumab Q2W and placebo, respectively
- 87% power to detect a difference of 17% between dupilumab Q4W treatment and placebo treatment (both in combination with TCS) in the percentage of patients who achieve an IGA score 0 or 1 at week 16, assuming that the percentages are 22% and 5% for dupilumab 300 mg Q4W and placebo, respectively
- 99% power to detect a difference of 51% in the percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 68% and 17% for dupilumab Q2W and placebo, respectively, (both in combination with TCS)
- 99% power to detect a difference of 45% in percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 62% and 17% for dupilumab Q4W and placebo, respectively, (both in combination with TCS)

The significance level is set to 2-sided, 0.05 level. The assumptions used for the power calculations were estimated based on results from the R668-AD-1224 study (phase 3 combination study 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 is similar to dupilumab 300 mg Q2W. In the absence of data of dupilumab in pediatric patients with AD, the data observed in the adult studies R668-AD-1224 and R668-AD-1021 are used for these sample size calculations. This is a conservative assumption as it is expected that the effect of dupilumab in children will be greater than that seen in adults. Children have disease for a shorter duration than adults and the disease is more Th2 driven in acute phase while it becomes more type 1 helper T cell in chronic phase (Thepen 1996, Gittler 2012). In addition, children with AD in general respond better to systemic therapies than adults (Schmitt 2007). A recent study compared the differences between activated and polarized T-cell subsets in blood of adult and pediatric patients with AD. The study found that AD is Th2 dominated in children while it extends to additional helper T cell subsets, particularly Th22, in adults (Czarnowicki 2015). The sample size calculations were done using nQuery (7.0).

Due to an inadvertent operational error, 68 patients were potentially unblinded. Details about the error and why it may have been unblinding are not included in the protocol but will be described in the clinical study report. An additional approximately 90 patients will be 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.

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

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

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

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.3. Pharmacokinetic Analysis Sets

The PK analysis set includes all randomized patients who received any study drug and who had at least 1 non-missing drug concentration result following the first dose of study drug.

10.3.4. Analysis Set for Anti-Drug Antibody Data

The ADA analysis set includes all treated patients who received any study drug and who had at least 1 non-missing ADA result (either "ADA negative" or "ADA positive") after the first dose of study drug.

10.4. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- 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 discontinued the study, and the reasons for discontinuation
- The total number of patients potentially unblinded
- A listing of patients treated but not randomized, patients randomized but not treated and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation
- A listing of potentially unblinded patients

10.5. Statistical Methods

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

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

All data will be summarized by 3 treatment groups (ie, dupilumab Q2W dose, dupilumab Q4W dose, and placebo). All placebo patients will be pooled for analysis regardless of whether it is 100 mg placebo, 200 mg placebo, or 300 mg placebo.

10.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group.

10.5.2. Efficacy Analyses

For each dose regimen and all efficacy variables, the analysis will be comparisons of each of the dupilumab treatment groups with the placebo group (Q2W and Q4W combined).

A sensitivity analysis for the primary endpoint and selected secondary endpoints will be performed in the mFAS.

10.5.2.1. Primary Efficacy Analysis

The Cochran-Mantel-Haenszel test adjusted by randomization strata (baseline weight group and region) will be used for analyzing the 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 checked, and if it is not met, sensitivity analyses including each stratification factor separately in CMH test will be conducted.

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

To account for the impact of rescue treatment on the efficacy effect: For the primary efficacy endpoints (which are binary efficacy endpoints), if rescue treatment is used (see Section 7.3), the patient will be specified as a nonresponder from the time the rescue is used.

If a patient withdraws from study, this patient will be counted as a nonresponder for endpoints after withdrawal.

Sensitivity analysis using the last observation carried forward (LOCF) approach 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. The efficacy data will be set to missing after rescue treatment is used, then the LOCF method will be used to determine patients' status at week 16.

In addition, the Cochran-Mantel-Haenszel method adjusted by randomization strata will also be performed on all observed data regardless if rescue treatment is used. A patient with missing data will be counted as a non-responder. Other sensitivity analyses may be conducted.

10.5.2.2. Secondary Efficacy Analysis

For binary endpoints, the secondary efficacy analysis will use the same approach as that used for the primary analysis.

For continuous endpoints:

- The multiple imputation (MI) with analysis of covariance (ANCOVA) model will be used as the primary analysis method. Patients' efficacy data through week 16 after the rescue treatment use will be set to missing first, and then be imputed by the multiple imputation method. Missing data from the FAS will be imputed 40 times to generate 40 complete datasets 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.
  - 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.
- The week 16 data of each of the 40 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (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.
- If a patient receives rescue treatment, the efficacy data collected after rescue treatment is initiated will be treated as missing. All efficacy data will be used for analysis regardless of whether the patient is on study treatment or discontinues the study treatment but remains in the study.
- In addition to the MI method described above, sensitivity analyses such as ANCOVA model with LOCF, MI method with ANCOVA model on all observed data regardless of rescue use will be conducted. Additional details on sensitivity analyses will be provided in the SAP.

Time to event endpoint will be analyzed using the Cox proportional hazards model. Kaplan-Meier curves will also be provided.

10.5.2.3. Multiplicity Considerations

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 vs placebo. The abbreviated, preliminary plan for hierarchical testing order for the primary endpoint and key secondary endpoints is shown in Table 3. The complete hierarchy including all the secondary endpoints will be provided in the SAP.

Table 3: Preliminary Statistical Hierarchy for Multiplicity Control

	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	5	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	6	2
Key Secondary endpoints	Percent change in EASI score from baseline to week 16	7	3
	Percent change from baseline to week 16 in weekly average of daily worst itch score	8	4

10.5.2.4. First-Step Analysis

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 specified in Section 4.2.1 and Section 4.2.2 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.

If a decision is made to perform the first-step analysis, in order to maintain study integrity with respect to the post-treatment follow-up visits, safety visits and analyses, 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.

10.5.3. Safety Analysis

Safety analysis will be based on the SAF. This includes reported TEAEs, AESIs, and other safety information (eg, clinical laboratory evaluations, vital signs, and 12-lead ECG results). A summary of safety results for each treatment group will be presented. In addition, safety data for the placebo Q2W group and placebo Q4W group will be summarized separately.

10.5.3.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to end of study. The treatment-emergent period includes the 16-week treatment period and follow-up period.
  - Treatment period: date of the first dose of study drug to week 16 visit date (study day 113 starting from the first dose of study drug if week 16 visit date is unavailable) or early termination date, whichever comes first.
  - Follow-up period: date after week 16 visit date (study day 113 starting from first dose of study drug if week 16 visit date is unavailable) to end of study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a preexisting condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group for overall during the treatment-emergent period, during the 16-week treatment period, and during the follow-up period will include:

- The number (n) and percentage (%) of patient with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.5.3.2. Other Safety

Vital Signs

Vital signs (sitting blood pressure, heart rate, respiration, and temperature) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

The number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each vital sign variable. The criteria for treatment emergent PCSV will be defined in the SAP.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

The number and percentage of patients with a treatment-emergent PCSV will be summarized for each clinical laboratory test. The criteria for treatment-emergent PCSVs will be defined in the SAP.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

10.5.3.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment group and 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 number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, standard deviation, minimums, Q1, medians, Q3, and maximums.

A summary of the number of doses by treatment group will be provided.

10.5.3.4. Treatment Compliance

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) × 100%

The treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

10.5.4. Analysis of Drug Concentration Data

No formal statistical analysis will be performed. Trough functional dupilumab concentration in serum ($C_{trough.timepoint}$) will be summarized at each time point using descriptive statistics. The data may be combined with data from other pediatric studies as well as adult studies, as applicable, for analysis using population methods. Any population PK analysis will be reported separately.

10.5.5. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 4.4 will be summarized using descriptive statistics by treatment group. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

10.5.6. Analysis of Biomarker Data

All exploratory biomarker data analyses will be performed on the FAS and no multiplicity adjustment is planned. Analyses of exploratory measures will be provided in the SAP.

10.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment will be the latest, valid pre-first-dose assessment available

General rules for handling missing data:

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

10.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) tool.

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization for sample collection schedules for dupilumab concentration and ADA, study drug supply
- EDC system – data capture
- SAS – statistical review, analysis, and reporting
- ARISg – a pharmacovigilance and clinical safety software system (Regeneron)
- AWARE, Business Objects XI – pharmacovigilance activities (Sanofi)

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required electronic CRFs must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the electronic CRF will be entered in the electronic CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs/IAFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

14.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF/IAF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF/IAF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed assent from each patient and written informed consent from each patient's parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to fullest possible extent in language that the patient (if applicable) and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF, and the IAF be signed and dated by the patient (if applicable) and the same investigator or designee who explained the IAF.

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF or a separate IAF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients/parents or legal guardians who can write but cannot read will have the assent/consent form read to them before writing their name on the form.
- Patients/parents or legal guardians who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the IAF/ICF to confirm that informed consent was given.

The original IAF/ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed IAF/ICF must be given to the patient/patient's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, the ICF/IAF must be reviewed and updated appropriately. All study patients and their parent(s) or legal guardian(s) must be informed of the new information and provide their written assent (if applicable) or consent if they wish the patient to continue in the study. The original signed revised ICF/IAF must be maintained in the patient's study record and a copy must be given to the patient/patient's parent(s) or legal guardian(s).

14.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by their initials and a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF/IAF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF/IAF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF/IAF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF/IAF without an IRB/EC-approved amendment. Regulatory approvals will also be obtained where required by local legislation.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

The end of the study will be when the last patient completes the last visit as per schedule of events.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs/IAFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF DUPILUMAB ADMINISTERED CONCOMITANTLY WITH TOPICAL CORTICOSTEROIDS IN PATIENTS ≥6 TO <12 YEARS OF AGE, WITH SEVERE ATOPIC DERMATITIS, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG

Is there a reasonable possibility that the event may have been caused by the study drug?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a known response to the study drug based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug is resumed
- are known to be a response to the study drug based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

APPENDIX 2. IGA SCALE

Please refer to the instructions below and place a checkmark next to the appropriate score below:

_____ **0 Clear**
_____ **1 Almost Clear**
_____ **2 Mild Disease**
_____ **3 Moderate Disease**
_____ **4 Severe Disease**

_____	_____	_____
Print Name (First/Last) of Investigator Completing Assessment	**Signature**	**Date**

Instructions:
The Investigator's Global Assessment is a static 5-point measure of disease severity based on an overall assessment of the skin lesions.

IGA: Disease Severity Scale and Definitions of the scoring:

Score	Investigator's Global Assessment (IGA) Standard Definitions	Investigator's Global Assessment (IGA): Proposed Morphological Descriptors
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive

4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

APPENDIX 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.

Category	Description of Protocol Deviation
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
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 immune-compromised status, as judged by the investigator

Category	Description of Protocol Deviation
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).

Category	Description of Protocol Deviation
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	V19/EOT or Early Termination visit not performed (protocol deviation not applicable for patients who completed EOT and rolled over to OLE)
Visit performed out of window	Visit 2 (TCS Standardization) visit is not within Days (-14 to -1) prior to Visit 3 (Baseline)
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

Category	Description of Protocol Deviation
Procedure not performed	Serum Pregnancy testing not performed at Screening (must check WOCBP at Screening visit: if Yes, for WOCBP then must have results)
Procedure not performed	Pregnancy testing not performed at Baseline, Visits 5, 7, 11, 15, 22/EOS or ET (must check WOCBP at Screening visit: if Yes, for WOCBP then must have results).
Procedure not performed	HIV, HBsAg, HBsAb, HBcAb and Hepatitis C Ab not performed at Screening visit
Procedure not performed	Hematology not performed at Screening or Baseline/Day 1
Procedure not performed	Chemistry not performed at Screening or Baseline/Day 1
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 within 12 months of screening
Procedure not performed	More than 1 scheduled study drug administration missed
Dosing non compliance	Study drug given to patient 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 patient due to incorrectly entered weight group in IVRS
Handling of Investigational Product was not performed in accordance with the protocol	Investigational product (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

Category	Description of Protocol Deviation
Handling of Investigational Product was not performed in accordance with the protocol	Patient was dosed with IP that had a temperature excursion and was deemed unacceptable
Inadequate Informed Consent administration	Incorrect ICF (unapproved version, incorrect version, incorrect study, not patient's language)
Inadequate Informed Consent administration	ICF not signed by patient/parent, ICF not dated by patient/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	Patient 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	Patient laboratory not reviewed to confirm eligibility by PI
Personnel not qualified and/or designated to perform study-related activities.	Patient 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 based on country requirements)
Randomization error-Patient Randomized to wrong treatment	Patient was randomized and treated with study drug from the incorrect treatment group
Randomization error-Patient Randomized to wrong treatment	Ineligible patient 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: ePRO compliance	0 = or lesser than 60% compliance NRS
Other: ePRO compliance	0 = or lesser than 60% compliance TCS
Other: ePRO compliance	0 = or lesser than 60% compliance moisturizer.
Other: ePRO compliance	TCS not applied for at least 11 of 14 days consecutively prior to randomization.
Other: Laboratory	Expired lab kits used

Category	Description of Protocol Deviation
Other: Laboratory	Improper collection/processing/shipping of Serum pregnancy, Urine pregnancy or HIV, HBsAg, HBsAb, HBcAb and Hepatitis C Ab lab samples
Other: Laboratory	Improper collection/processing/shipping of Hematology or Chemistry lab samples at Screening and Baseling visits
Other: Laboratory	Serum pregnancy, Urine pregnancy or HIV, HBsAg, HBsAb, HBcAb and Hepatitis C Ab lab samples were beyond stability and no results available.
Other: Laboratory	Hematology or Chemistry lab samples at Screening or Baseling visits were beyond stability and no results available.
Other: AESI	AESI not reported within protocol defined window
Other: SAE	SAE not reported within protocol defined window

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the conduct of the study.

Study 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 Number: R668-AD-1652, Amendment 3

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00053769 v2.0

ESig Approval	[redacted]gement 21-Nov-2018 16:35:11 GMT+0000
ESig Approval	[redacted] 21-Nov-2018 16:54:07 GMT+0000
ESig Approval	[redacted] 21-Nov-2018 18:16:44 GMT+0000
ESig Approval	[redacted] 21-Nov-2018 18:36:09 GMT+0000

Signature Page for VV-RIM-00053769 v2.0 Approved