	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.

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

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

- 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).

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												

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

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

[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)

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.

	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

8.1.1. Footnotes for Schedule of Events Table

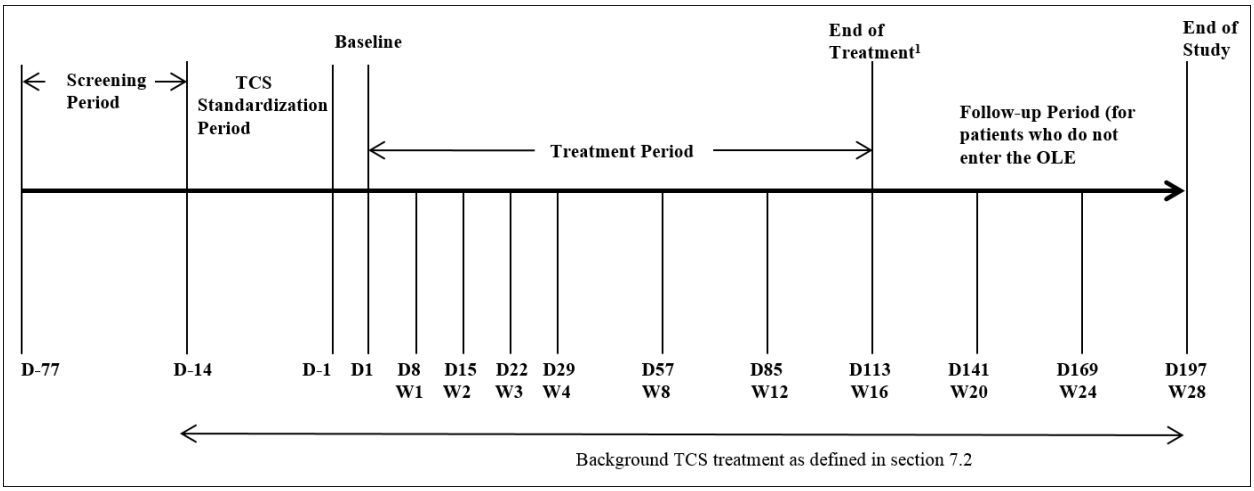
8.1.1.1. Footnotes for Schedule of Events Table 1

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.

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.

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

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.

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,

(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

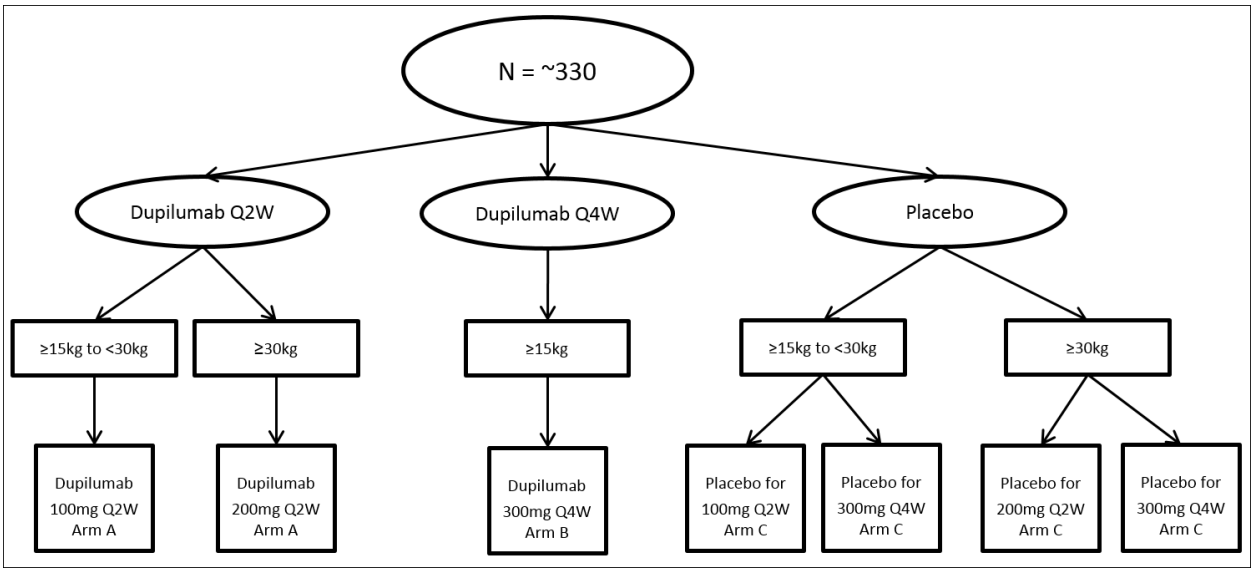
Study R668-AD-1412 was a phase 2a, multicenter, open-label, ascending-dose, sequential-cohort study investigating the safety, tolerability, PK, immunogenicity, and efficacy of single-dose and repeat-doses of dupilumab administered SC in pediatric patients with moderate to severe AD (for adolescents ≥12 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.

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.

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.

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.

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.

10.5.5. 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.

	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

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.

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