Study Design

This study is a 2-part (parts A and B) phase 2/3 study to evaluate the safety, PK, and efficacy of dupilumab in patients 6 months to less than 6 years of age with severe AD (part A), or moderate to severe AD (part B).

Part A

Part A of the study will be an open-label, single-ascending dose, sequential cohort study investigating the PK, safety and efficacy of a single dose of SC dupilumab in pediatric patients with severe AD (children aged ≥6 months to <6 years of age).

Two sequential age cohorts are planned in part A: age cohort 1 (≥2 to <6 yrs old) and age cohort 2 (≥6 months to <2 yrs old). Within each age cohort, approximately 10 patients will be enrolled in each of the 2 dose sub-cohorts: sub-cohort A (3 mg/kg) and sub-cohort B (6 mg/kg). Enrollment and study dosing will start with cohort 1A (≥2 to <6 yrs old, 3 mg/kg dose, n=10). Following safety review of data from cohort 1A, enrollment will start in both cohort 1B (≥2 to <6 yrs. old, 6 mg/kg dose, n=10) and cohort 2A (≥6 months to <2 yrs old, 3 mg/kg dose, n=10). Following safety review of data from cohort 2A, enrollment will start in cohort 2B (≥6 months to <2 yrs old, 6 mg/kg dose, n=10).

Part A of the study will consist of a screening period (day -35 to day -1), a baseline visit (day 1), a single-dose treatment followed by a 4-week PK sampling period, and an additional 4-week follow-up period (only for patients who decline to participate in a subsequent open-label extension [OLE] study). After informed consent is provided by patients' parents or legal guardians, patients will be assessed for study eligibility at the screening visit. Patients who meet eligibility criteria will undergo baseline assessments and then proceed to part A to receive their single dose of study treatment on day 1 and undergo functional dupilumab PK sample collection during the following 4 weeks for characterizing the single-dose PK profile.

All patients will be offered an opportunity to participate in the OLE study at week 4. Patients who decline will be followed up for an additional 4 weeks (total of 8 weeks). This will ensure a sufficient follow-up period for these patients and will maximize patient safety.

Concomitant use of TCS with or without topical calcineurin inhibitors (TCIs) will be permitted during part A of the study.

Part B

Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled study in which dupilumab will be administered concomitantly with TCS to patients ≥6 months to <6 years of age with moderate-to-severe AD. Part B will consist of a screening period of up to 56 days (including 2 weeks of TCS standardization), a treatment period of 16 weeks, and a follow-up period of up to 12 weeks. Patients who enrolled in part A of the study are not eligible to participate in part B. After informed

EDC	Electronic data capture
e-diary	Electronic diary
EOS	End of study
EOT	End of treatment
ET	Early termination
EU	European Union
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
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IDQOL	Infants' Dermatology Quality of Life Index
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IPV	Inactivated polio vaccine
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LOQ	Limit of quantitation
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

In initial interactions with a Competent Authority which were held at a time when there was no data from clinical studies on the use of dupilumab in the pediatric population, the sponsor was advised to limit the patient population to severe patients in patients <12-years-old. Since then, dupilumab has been tested in multiple clinical studies in pediatric patients and shown to provide considerable clinical benefit to pediatric patients with an acceptable safety profile. Subgroup analysis from dupilumab phase 3 studies in both adult and adolescent patients showed comparable efficacy and safety profile patients with moderate and severe disease at baseline. Moreover, an analysis performed on patients ≥6 to <12 years of age in the open-label extension study with a baseline disease of moderate severity (IGA=3) showed that the drug was well tolerated in this subpopulation with a comparable safety profile to the overall study population. The sponsor was recently advised to broaden the patient population to moderate-to-severe disease by the United States Food and Drug Administration. This approach will maximize the number of patients that will benefit from this drug and also facilitate enrollment in this study.

An add-on study design will ensure that patients who are randomized to the placebo group will continue to receive standard treatment for their disease; an important consideration given the target population consists of infants and young children with moderate-to-severe disease. Moreover, this approach mirrors the therapeutic paradigm envisaged for dupilumab post approval in this age-group. Clinicians are expected to continue treatment with topical therapies upon initiation of dupilumab, and to taper use of topical treatment following onset of clinical effect of dupilumab.

The 16-week treatment duration is similar to what was used in the adult pivotal trials (R668-AD-1416 and R668-AD-1334). Patients were treated with dupilumab every 2 weeks [Q2W] dose regimen for 52 weeks in another adult phase 3 study (R668-AD-1224) and no incremental therapeutic benefit was noticed for the overall patient population between week 16 and week 52. Treatment duration of 16 weeks has been chosen because the maximum, or close to maximal, therapeutic effect for dupilumab in this patient population is expected to be achieved by this time based on data from these studies and also from R668-AD-1526 (phase 3 study of dupilumab in adolescent patients with AD. Data gathered from the dose-range-finding study in adults (R668-AD-1021) showed that all dosing regimens (100 mg every 4 weeks [Q4W], 200 mg QW, 200 mg Q2W, 300 mg Q2W, 300 mg Q4W) achieved steady-state concentration on or before week 16. These findings suggest that 16 weeks will be sufficient time for the selected doses for part B (fixed dosing tiered by body weight strata: 200 mg Q4W [≥5-<15 kg] and 300 mg Q4W [≥15-<30 kg]) to achieve steady-state concentration and saturation of the target-mediated pathway. The 12-week follow-up period is based on the expected PK of dupilumab after the last dose, ie, the time for systemic concentrations to decline to non-detectable levels (below the lower limit of quantification) in most patients.

The co-primary endpoints (proportion of patients with Investigator Global Assessment (IGA) 0/1 and ≥75% improvement from baseline in Eczema Area and Severity Index [EASI] score [EASI-75] at week 16) (proportion of patients with EASI-75 is a co-primary endpoint for EU and EU Reference Market Countries only, key secondary endpoint for US) were chosen because they are similar to those used in the adult pivotal studies (SOLO trials), and to address the varying primary endpoint requests by differing health authorities. Eczema Area and Severity Index has been validated in the pediatric population in a prior study (Barbier 2004).

The approach to combine parts A and B into a single study will ensure earlier availability of a potentially effective therapy in a target population with high unmet medical need.

Part A

Part A of the study will be an open-label, single ascending-dose, sequential cohort study investigating the PK, safety, and efficacy of a single dose of SC dupilumab in pediatric patients with severe AD (children aged ≥6 months to <6 years of age).

Study cohorts will only be used in part A of the study. Two sequential age cohorts are planned in part A: age cohort 1 (≥2 to <6 yrs. old) and age cohort 2 (≥6 months to <2 yrs. old). Within each age cohort, approximately 10 patients will be enrolled in each of the 2 dose sub-cohorts: sub-cohort A (3 mg/kg) and sub-cohort B (6 mg/kg). Enrollment and study dosing will start with cohort 1A (≥2 to <6 yrs. old, 3 mg/kg dose, n=10). Following safety review of data from cohort 1A, enrollment will start in both cohort 1B (≥2 to <6 yrs. old, 6 mg/kg dose, n=10) and cohort 2A (≥6 months to <2 yrs. old, 3 mg/kg dose, n=10) (see details in Section 3.1.2 and Figure 4). Following safety review of data from cohort 2A, enrollment will start in cohort 2B (≥6 months to <2 yrs. old, 6 mg/kg dose, n=10).

To ensure adequate representation of patients from all age-groups, a cap will be placed on the number of patients that will be enrolled in each of the dose sub-cohorts (3 mg/kg and 6 mg/kg) as follows:

Cohorts 1A and 1B:

- 2 years to <4 years of age: 7 patients
- 4 years to <6 years of age: 7 patients

Cohorts 2A and 2B:

- 6 months to <1 year of age: 7 patients
- 1 year to <2 years of age: 7 patients

Part A of the study will consist of a screening period (day -35 to day -1), a baseline visit (day 1), a single-dose treatment followed by a 4-week PK sampling period (Figure 2), and an additional 4-week follow-up period (only for patients who decline to participate a subsequent OLE study). After informed consent is provided by patients' parents or legal guardians, patients will be assessed for study eligibility at the screening visit. Patients may be rescreened if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure is related to failing the inclusion criteria for disease severity. Patients who meet eligibility criteria will undergo baseline assessments and then proceed to part A to receive their single dose of study treatment on day 1 and undergo functional dupilumab PK sample collection during the following 4 weeks for characterizing the single-dose PK profile. All patients will be offered an opportunity to participate in an OLE study at week 4. Patients who decline will be followed up for an additional 4 weeks (total of 8 weeks). This will ensure a sufficient follow-up period for these patients and will maximize patient safety.

Concomitant use of TCS with or without TCIs will be permitted during part A of the study, including the screening period (Section 5.2). Investigators will be instructed to standardize the use of topical steroids to medium, and/or low potency, and ensure that the use of TCS is consistent with product labels. The use of high-potency TCS is not allowed (except for rescue).

Table 1: Schedule of Events for the Screening, Single-Dose Treatment and PK Sampling Period (Part A)

Study Procedure	Screening Period	Single-dose Treatment and PK Sampling Period					Additional Follow-Up Period[8]			
	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Unscheduled Visit[7]	Early Termination Visit
Week				1	3	4	6	8		
Study Day(s)	-35 to D-1	1	3	8	18	29	43	57		
Visit window (days)				±3	±3	±3	±3	±3		
Screening/Baseline:										
Inclusion/Exclusion	X	X								
Parental Informed Consent	X									
Parental Informed Consent for Optional Genomic Study[1]	X									
Medical History	X									
Demographics	X									
Treatment[3]:										
Administer Study Drug		X[2]								
Concomitant Meds and Procedures	X	X	X	X	X	X	X	X	X	X
Efficacy[3]										
Assessment of Pruritus, IGA, EASI, SCORAD, BSA	X	X			X	X	X	X	X	X
Safety[3]:										
Weight	X	X				X				X
Height	X									
Vital Signs	X	X[2]	X	X	X	X	X	X	X	X
Physical Examination	X							X	X	X
Electrocardiogram	X					X			X	X
Adverse Events	X	X[2]	X	X	X	X	X	X	X	X

6.2.2. Efficacy Procedures

A variety of parameters will be collected during parts A and B of the study to assess efficacy/effectiveness of dupilumab, including measures of AD severity, use of concomitant treatment for AD, and parent/caregiver-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 investigator site binder for instructions on the administration and use of all patient-reported instruments (including Assessments of Pruritus [worst scratch/itch], Skin Pain, and Sleep Diary, CDLQI, Infants' Dermatology Quality of Life Index [IDQOL], Dermatitis Family Index [DFI], Caregiver Missed Workdays, and POEM, Caregiver Global Impression of Disease [CGID], Caregiver Global Impression of Change [CGIC], Pediatric Asthma Symptom Questionnaire [PASQ], and Caregiver-Reported Nasal Symptom Questionnaire [CNSQ]).

Instructions for taking photographs (in part B only) are provided in the photography reference manual.

6.2.2.1. Assessment of Pruritus

For part A, pruritus (scratch/itch) will be assessed by the parent/caregiver using a NRS at time points listed in Section 6.1, Table 1. The parents/caregivers will be asked "On a scale of 0 to 10, with 0 being 'no itch/scratching' and 10 being the 'worst itch/scratching imaginable', how would you rate your child's itch during the past 24 hours?"

Itch will be measured during part B using a worst scratch/itch NRS that was developed and tested for the study-relevant age group. This is an 11-point scale (0 to 10) in which 0 indicates no scratching/itching while 10 indicates worst scratching/itching possible. The parents/caregivers will be asked to:

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

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

For part B, pruritus will be assessed by the parent/caregiver on a daily basis using an e-diary throughout the entire study (ie, screening, treatment, and follow-up periods; see Table 2).

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

6.2.2.12. 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 young children, the head and neck (H), upper extremities (U), trunk (T), and lower extremities (L) are assigned proportionate body surface areas of 20% (H), 20% (U), 30% (T), and 30% (L), roughly consistent with the 'rule of nines". 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 6.1, Table 1 (Part A), and Table 2 (Part B).

The EASI assessment tool is provided in the investigator site binder.

6.2.2.13. 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 in children. Patients will undergo this assessment at time points according to Section 6.1, Table 1 (Part A), and Table 2 (Part B).

The BSA assessment tool is provided in the investigator site binder.

Note: The proportion assigned to different body regions varies by age in young children.

6.2.2.14. 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) with the Global Individual Signs Score (GISS) using the EASI severity grading criteria. The GISS **will only be assessed during part B** at time points listed in Table 2 (Part B).

The GISS assessment tool is provided in the investigator site binder.

6.2.2.15. SCORing Atopic Dermatitis

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (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 6.2.2.13) 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 parent/caregiver or relative on a Visual Analogue Scale, where 0 is no itch (or sleeplessness) and

6.2.2.19. Caregiver-Reported Nasal Symptom Questionnaire

The CNSQ will be used to assess the effect of study drug on symptoms of allergic rhinitis. The summed score will include the following 4 symptoms: runny nose, nasal congestion, nasal itching, and sneezing, each rated on a 0 to 3 scale of severity. The questionnaire will be completed only for the subset of patients with a medical history of allergic rhinitis. It is to be completed by the child's parent or caregiver who fluently speak a language in which the questionnaire is presented (based on availability of translations in participating countries).

Caregivers will be instructed on using the e-diary to record the CNSQ during the screening period (for the 14 days before baseline/day 1) and for the 7 days preceding visits 7, 19, and 22 (weeks 4, 16, and 28) (see Table 2 [Part B]).

6.2.3. Safety Procedures

6.2.3.1. Vital Signs

Vital signs (including sitting systolic and diastolic blood pressure, heart rate, respiration, and temperature) will be collected pre-dose at every in-clinic visit.

During part A, at the baseline visit, patients will be monitored at the study site for a minimum of 2 hours after study drug administration. Vital signs (systolic and diastolic blood pressure, heart rate, respiration, and temperature) and AE assessments will be performed at 30 minutes (±10 minutes) post-injection and then at 2 hours (±15 minutes) post-injection. See Section 6.1, Table 1 (Part A), for assessment time points.

During part B, patients will be monitored at the study site at certain dosing visits for a minimum of 2 hours after study drug administration. Vital signs (systolic and diastolic blood pressure, heart rate, respiration, and temperature) and AE assessments will be performed at 30 minutes (±10 minutes) post-injection, and at 2 hours (±15 minutes) post-injection. See Section 6.1, Table 2 (Part B), for assessment time points.

6.2.3.2. Body Weight and Height

Body weight and height will be measured at time points according to Section 6.1, Table 1 (Part A), and Table 2 (Part B).

6.2.3.3. Physical Examination

A thorough and complete physical examination will be performed at visits according to Section 6.1, Table 1 (Part A) and Table 2 (Part B). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

6.2.3.4. 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 6.1, Table 1 (Part A), and Table 2 (Part B). 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.

6.2.3.5. Laboratory Testing

Hematology and serum chemistry 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 6.1, Table 1 (Part A), and Table 2 (Part B).

Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol[2]
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (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 [LDL] and high-density lipoprotein [HDL])
3 CPK isoenzymes will be measured when CPK >2.5× the ULN

Hematology

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

Other Laboratory Tests

The following tests will be performed at screening according to Section 6.1, Table 1 (Part A), and Table 2 (Part B): 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).

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 7.2.5.

Serum samples for measurements of biomarkers (including TARC, total IgE, immunoglobin profiling, antigen-specific IgE, 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 6.1, Table 1 (Part A), and Table 2 (Part B).

6.2.6. Vaccine Response - Optional

Humoral immune responses to standard vaccines administered as part of the routine immunization schedule occurring during treatment with dupilumab, will be evaluated for those patients eligible for these vaccinations in part B of the study.

Parents/caregivers will be encouraged to provide vaccination plans at screening for any vaccines that are planned to be administered to the patient, in accordance with the patient's age, local medical practice and immunization schedule, during the study. Inactivated vaccines are permitted during the study. Live attenuated vaccines are excluded during the study. Parents or legal guardians who agree for their child to participate in the optional vaccine response sub-study will be required to sign a separate vaccine-response sub-study ICF for the collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine administered; one sample will be drawn before administration of the vaccine and the second sample after administration of the vaccine.

The first sample (pre-vaccination) may be drawn at any time up to 6 weeks prior to the scheduled vaccination. The second sample should preferably be drawn 3 to 4 weeks (maximum up to 6 weeks) after vaccination. Blood collections should be conducted at regularly scheduled study visits but if this is not feasible, the samples may also be collected at unscheduled visits. Details on the date(s) of vaccination and the specific vaccines administered (ie, brand and antigenic strains) should be collected on the Vaccination Record Form.

The humoral response endpoints will be described in the statistical analysis plan (SAP).

Patients who do not get an adequate response to vaccine administration during part B of the study may be offered re-vaccination during the OLE. The clinical study sites will be provided with post-vaccination titers only at the completion of the study due to risk of unblinding of this study. The determination of whether re-vaccination is needed will be made on a case-by case basis based on the titer results and the clinical relevance of these results. The investigator may consult with the primary physician/ pediatrician of the patient to determine the further course of action on these patients. The investigator may also report the cases of inadequate response as AEs, based on criteria in Section 7.1 of the protocol.

7.2. Recording and Reporting Adverse Events

7.2.1. 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 investigator site binder for the procedures to be followed.

Information on follow-up for AEs is provided in Section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.2.5.

7.2.2. 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 investigator site binder 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/Ethics Committee (IRB/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.

7.2.3. 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.

Adverse Events of Special Interest: AESI must be reported within 24 hours of identification. AESIs for this study include:

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

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

Refer to the investigator site binder for the procedures to be followed.

7.2.4. 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 investigator site binder for the procedures to be followed.

7.2.5. 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 7.3.1.

7.2.6. Follow-up

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

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

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

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

- **Mild:** Causes no or minimal interference with age appropriate daily activities. No intervention needed.
- **Moderate:** Causes more than minimal interference with age appropriate daily activities. Local or non-invasive intervention indicated.
- **Severe:** Causes inability to perform age appropriate daily activities. Hospitalization or invasive intervention indicated.

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

7.3.2. Evaluation of Causality

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 adverse event 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 investigator will also assess whether the AEs are related to any study procedures (as listed in Table 1 and Table 2).

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

7.4. 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 medical 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.

7.5. 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).

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Demographic characteristics will include variables such as age, race, weight, height, etc. Baseline characteristics will include variables such as disease severity, medical history, medication history, etc for each patient.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoints

The primary endpoints in part A of the study are:

- Concentration of total dupilumab in serum over time and PK parameters (summary statistics of drug concentration and PK parameters)
- The incidence and severity of treatment-emergent adverse events (TEAEs) through the end of part A.

The primary endpoint in part B of the study is:

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

The co-primary endpoints in part B of the study are (**only in the EU and EU Reference Market Countries**):

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

8.2.2. Secondary Endpoints

The secondary endpoints in part A are:

- The incidence of SAEs and severe TEAEs to week 4
- Percent change in EASI score from baseline to week 4
- Percent change in SCORAD score from baseline to week 4
- Proportion of patients with an IGA score of either 0 or 1 (on a 5-point scale) at week 4

Immunogenicity will be addressed by the ADA parameters described in Section 8.4.

The key secondary endpoints in part B are:

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

Other secondary efficacy endpoints in part B are:

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

- Mean of caregiver missed workdays from baseline to week 16
- Incidence of skin infection TEAEs (excluding herpetic infections) through week 16
- Incidence of SAEs through week 16

8.2.3. Other Endpoints and Assessments

Other endpoints and assessments, as applicable, will be specified in the SAP.

8.3. Pharmacokinetic Variables

The PK variable is the concentration of functional/total dupilumab at each time point. Samples in this study will be collected using a sparse sampling schedule, eg, only 1 blood sample for drug concentration measurement is collected at any single clinic visit. These sampling timepoints are specified in Table 1 (part A) and Table 2 (part B).

8.4. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time-point/visit. Samples in this study will be collected at the clinic visits specified in Table 1 (part A) and Table 2 (part B).

8.5. Vaccine Response Variables

For patients who receive vaccinations, vaccine response parameters will be summarized by treatment groups using descriptive statistics.

9. STATISTICAL PLAN

This section provides the basis for the 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 8.

9.1. Statistical Hypothesis

Part A of the study is open-label; therefore, no statistical hypotheses will be tested in this portion of the study.

For part B of the study, the following null hypothesis and alternative will be tested for the dupilumab treatment group:

H0: There is no treatment difference between dupilumab and placebo

H1: There is a treatment difference between dupilumab and placebo

Baseline weight group, baseline disease severity (IGA=3, 4), and region/country will be the 3 stratification factors for patient randomization that will be accounted for in the statistical modeling for efficacy.

9.2. Justification of Sample Size

In part A of the study, the sample size of 40 patients was empirically based on the number of patients required to adequately characterize the safety/PK profile in this population.

For part B of the study, it is estimated that a sample size of 160 patients (80 patients per treatment group), at the 2-sided 5% significance level, will provide the following:

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

The assumptions used for the above power calculations were based on results from patients in the R668-AD-1652 study (phase 3 combination study for patients ≥6 to <12 years of age with severe AD). As outline in Section 1.2.2, the tiered fixed-dose regimen (200 mg Q4W in patients ≥5-<15 kg, 300 mg Q4W in patients ≥15-<30 kg) is expected to provided exposure comparable to that seen with 300 mg Q4W in patients ≥6 to <12 years of age or 300 mg Q2W in adult patients.

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

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

9.3. Analysis Sets

9.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients in part B; it is based on the treatment allocated (as randomized).

The per protocol set (PPS) includes all patients in the FAS, except for those who are excluded because of major protocol violations. A major protocol violation is one that may affect the interpretation of study results and will be reviewed and adjudicated by study team. A final list of major protocol violations will be generated prior to the primary database lock.

All efficacy variables for part B will be evaluated using the FAS. The primary efficacy endpoint will also be evaluated using the PPS. The analysis using the FAS will be considered primary.

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 will be provided separately for parts A and B. The summary will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 7.3.1), 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.

In addition, to account for potential differential exposure time, the exposure-adjusted analyses for part B may be provided. The details will be specified in the SAP.

9.5.3.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) 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.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for vital signs.

Laboratory Tests

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

Number and percentage of patients with a treatment-emergent PCSV will be summarized for each clinical laboratory test.

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.

Study Procedure	Screening Period	Single-dose Treatment and PK Sampling Period					Additional Follow-Up Period[8]			
	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Unscheduled Visit[7]	Early Termination Visit
Week				1	3	4	6	8		
Study Day(s)	-35 to D-1	1	3	8	18	29	43	57		
Visit window (days)				±3	±3	±3	±3	±3		
LaboratoryTesting[3,4]:										
Hematology	X	X				X		X	X	X
Blood Chemistry	X					X		X	X	X
HIV, HBsAg, HBsAb, HBcAb, Hepatitis C Ab, TB[5]	X									
Biomarker[6]:										
TARC		X				X				X
Total serum IgE		X				X				
Research Testing:										
Optional DNA sample[1]		X								
PK/Drug Concentration and ADA Samples:										
PK/Drug concentration sample[6]		X	X	X	X	X			X	X
ADA sample[6]		X		X		X			X	X

Note: AE = adverse event; BSA = body surface area; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IGA = Investigator Global Assessment; IgE = immunoglobulin E; PK = pharmacokinetic; SCORAD = SCORing Atopic Dermatitis; TARC = thymus and activation regulated chemokine; TB = tuberculosis.

[1] For patients who parents or legal guardians agree to their participation and provide a specific written informed consent for the optional genomics sub-study (DNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study.

[2] Patients will be monitored at the study site at visit 2 for a minimum of 2 hours after study drug administration. Vital signs and AE assessments will be done at 30 minutes (±10 minutes) post-injection, and then at 2 hours (±15 minutes) post-injection.

[3] Assessment/procedures should be conducted in the following order: patient-reported outcomes, investigator assessments, safety and laboratory assessments, administration of study drug.

[4] Samples to be collected prior to injection of study drug.

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

[6] Samples to measure functional dupilumab concentration, ADA, and biomarkers will be collected prior to injection of study drug. Patients who are ADA positive at their last study visit (early termination or end of study) and who do not participate in the OLE may be considered for follow-up based on the overall clinical presentation at that time. Patients who are considered for follow-up will be asked to return to the clinic to have additional samples collected for analysis.

[7] The specific assessments that will be performed at the unscheduled visit will depend upon the reason for the unscheduled visit.

[8] For patients who decline the subsequent open-label extension study.

Study Procedure	**Screening Period[24]**		**BL**	**Treatment Period**																	**Follow-Up**			**Un-scheduled Visit[21]**	**ET Visit**
	SCN	**TCS Std**				**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**		**PV[1]**	**PV[1]**	**PV[1]**	**EOT**			**EOS**		
Visit	**1**	**2**	**3**	**4**	**5**	**6[1]**	**7**	**8[1]**	**9**	**10[1]**	**11**	**12[1]**	**13[1]**	**14[1]**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		
Week	**-**	**-**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**		
Study Day(s)	**-56 to -15**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**		
Visit window (days)	**-**	**-**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Parental Informed Consent for Optional Use of Photographs (selected study sites only)[30]	X																							
Collect vaccination plan[4]	X																							
Medical History	X																							
Ophthalmology Exam (patients with history of certain eye disorders)[32]	X																							
Demographics	X																							
Randomization			X																					
Parent/ Caregiver e-diary training[5]	X	X																						

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An IDMC, composed of members who are independent from the sponsor and the study investigators, will monitor patient safety in parts A and B by conducting formal reviews of accumulated safety data. If requested, the IDMC may have access to 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 be informed about decisions made at the internal dose escalation review meetings and will be provided with a summary of the data analyzed during these meetings. Advice of IDMC may be sought by the internal safety monitoring team (SMT) regarding decisions to suspend dosing (see Section 3.1.2 for details). The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution. This committee 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 patient safety.

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

3.3.2. Dose Escalation Review Committee

The DERC will review data from part A of the study and will make decisions on dose escalation (see Section 3.1.2 for details).

The DERC will include the following core members: Regeneron Medical Monitor, Regeneron Risk Management Lead and designated Lead Principal Investigator. Other members of this committee will include, but will not be limited to, representatives from Clinical Trial Management, Biostatistics and Data Management, and Pharmacovigilance. Other individuals, including relevant site investigator(s), may be included as needed.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Part A of the study was conducted at multiple sites in North America and Europe. Part B of the study will be conducted at multiple sites in North America, Europe, Japan, and China.

For part A of the study, approximately 40 pediatric AD patients are planned to be enrolled in 4 cohorts. To adequately characterize the safety/PK profile of this population, a total of 10 patients in each of the following cohorts will be enrolled:

- Cohort 1A: ≥2 to <6 years of age, 3 mg/kg dose, n = 10
- Cohort 1B: ≥2 to <6 years of age, 6 mg/kg dose, n = 10
- Cohort 2A: ≥6 months to <2 years of age, 3 mg/kg dose, n = 10
- Cohort 2B: ≥6 months to <2 years of age, 6 mg/kg dose, n = 10

consent is provided by patients' parents or legal guardians, patients will be assessed for study eligibility at the screening visit. Assent will be collected from patient, if applicable, as per local regulatory (competent authority/ethics) guidelines, based upon the age and level of maturity of the patient. 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. Starting on day -14, all patients will be required to initiate treatment with a low potency TCS using a standardized regimen. Based on investigator discretion, low potency TCS may also be used on areas of thin skin. The use of TCIs will be permitted during the screening period except for the 2-week period leading up to the baseline visit.

During part B, patients will be required to apply moisturizers twice daily for at least 7 days before randomization (not including the day of 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 ratio stratified by baseline body weight (≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3, 4), and region/country (North America, Europe, Japan, and China) as follows:

- dupilumab (fixed dosing tiered by body weight every 4 weeks (Q4W): 200 mg Q4W for patients ≥5 to <15 kg or 300 mg for patients ≥15 to <30 kg Q4W.
- placebo Q4W.

The number of patients with moderate AD (IGA=3) will be capped at approximately 40.

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

After completion of the treatment period, patients will enter a follow-up period of 12 weeks (only for patients who do not participate in a subsequent OLE study). Follow-up visits for these patients will occur every 4 weeks from week 20 through week 28. During the follow-up period, patients will be monitored for safety and tolerability and have laboratory and clinical assessments.

Parts A and B

Safety and laboratory assessments, samples for dupilumab concentration and anti-drug antibody (ADA) response to dupilumab, neutralizing antibody (NAbs), and efficacy assessments will be performed or collected at specified time points throughout parts A and B of the study. Patients will also undergo sparse blood sample collection for characterizing the repeat-dose trough concentrations of dupilumab in serum during part B.

MI	Multiple imputation
NAb	Neutralizing antibody
NCA	Non-compartmental analysis
NRS	Numeric rating scale
ObsRO	Observation reported outcome
OLE	Open-label extension
PASQ	Pediatric Asthma Symptom Questionnaire
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per protocol set
POEM	Patient Oriented Eczema Measure
PRO	Patient reported outcome
PT	Preferred term
PV	Phone visit
Q1	First quartile
Q2W	Every 2 weeks
Q3	Third quartile
Q4W	Every 4 weeks
QOL	Quality of Life
QW	Once weekly
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SCN	Screening
SD	Standard deviation
SMT	Safety monitoring team

As the efficacy and safety of dupilumab for the treatment of AD has not yet been established in patients ≥6 months to <6 years, 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 concerns in patients randomized to the placebo group:

- Mandatory requirement for use of concomitant TCS
  - Starting on day -14 **(applicable to part B only)**, all patients will initiate a standardized TCS treatment regimen with a low-potency TCS that may be adjusted based on clinical response (see Section 5.2). 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: medium or high-potency TCS, systemic corticosteroids, nonsteroidal immunosuppressive drugs, and TCI (see Section 5.3).
- Open-Label Extension (OLE) Study
  - Patients who complete the treatment period of part B (week 16) will be offered an opportunity to screen for the OLE study at end-of-treatment (EOT) visit. Additional details concerning eligibility for the OLE can be found in Section 5.8.

As described in Section 3.3.1, an Independent Data Monitoring Committee (IDMC), will monitor patient safety by conducting formal reviews of accumulated safety data on a program-wide level.

1.2.2. Rationale for Dose Selection

In the adult phase 3 studies (SOLO-1 and SOLO-2, both studies had identical study designs), patients were randomized into 1 of 3 treatment groups: dupilumab 300 mg SC QW, dupilumab 300 mg SC Q2W, or placebo for 16 weeks following an initial dupilumab loading dose of 600 mg SC, or placebo. Both dose regimens of 300 mg QW and 300 mg Q2W provided significant clinical benefit and had an acceptable safety profile. For the 16-week treatment period, the overall rate of adverse events (AEs) (65% to 73% dupilumab and 65% to 72% placebo) was comparable between the dupilumab and the placebo groups. The rate of serious adverse events (SAEs) was 1% to 3% for dupilumab and 5% to 6% for placebo. Serious and severe infections were also numerically higher in the placebo groups in both studies (0.5% to 1% dupilumab and 2% to 3% placebo).

Assuming an average adult body weight of 75 kg, a dose of 4 mg/kg would be equivalent to 300 mg and would seem to provide matching dose levels in children. However, PK parameters, like clearance (CL) and volume of distribution (V), do not scale linearly with body weight for younger children (Zhang 2015). Therefore, the reductions of CL and V in children are less than weight-proportional. A weight-normalized dose directly scaled down from an adult dose is likely to yield sub-optimal exposure in children.

The use of TCI will be reserved for problem areas (eg, face, intertriginous, and genital areas) and only in children ≥2 years of age.

Safety and laboratory assessments, samples for dupilumab concentration, and efficacy assessments will be performed or collected at specified time points throughout part A of the study according to the schedule of events listed in Table 1. Anti-drug antibody assessments will be conducted at time points analyzed as listed in Table 1. Patient participation in the genomics sub-study in part A is optional. Samples for DNA analysis will be collected from patients whose parents or legal guardians agree to enroll in the optional sub-study and sign a separate genomics sub-study informed consent form (ICF) (see Section 6.2.7.3).

An OLE study (R668-AD-1434) in patients aged 6 months to <18 years old is currently ongoing. Patients who complete this study (ie, complete up to the end of study visit in part A [week 4]), may be eligible to enroll in this OLE study, in which they will receive treatment with dupilumab.

Part B

Part B of the study will be a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of SC dupilumab when administered concomitantly with TCS in pediatric patients, ≥6 months to <6 years of age, with moderate-to-severe AD. The number of patients with moderate AD (IGA=3) will be capped at approximately 40.

Part B of the study will consist of the following 3 periods: a screening period of up to 56 days (including 2 weeks of TCS standardization), a treatment period of 16 weeks, and a follow-up period of 12 weeks (Figure 3). Patients who enrolled in part A of the study are not eligible to participate in part B. After informed consent is provided by patients' parents or legal guardians, patients will be assessed for study eligibility at the screening visit. Assent will be collected from patients, if applicable, as per local regulatory (competent authority/ethics) guidelines, based upon the age and level of maturity of the patient. 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. Starting on day -14, all patients will initiate a standardized low potency TCS treatment regimen according to the guidelines in Section 5.2. The use of TCIs will be permitted during the screening period, except for the 2-week period leading up to the baseline visit. Patients may be rescreened twice if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure is related to failing the disease severity inclusion criteria.

Patients will be required to apply moisturizers twice daily for at least 7 days before randomization (not including the day of randomization) and continue throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

6.2.2.2. Assessment of Skin Pain

Skin pain will be assessed by the parent/caregiver at time points during part B according to Section 6.1, Table 2. Skin pain will be measured during part B using a skin pain NRS that was developed and tested for the study-relevant age group. This is an 11-point scale (0 to 10) in which 0 indicates no pain while 10 indicates worst pain possible. The parents/caregivers will be asked to:

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

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

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

6.2.2.3. Assessment of Sleep Quality and Other Sleep-Related Concepts Using Sleep Diary

A sleep diary will be completed by the parent/caregiver at time points during part B according to Section 6.1, Table 2 (Part B). The sleep diary includes 2 questions assessing the caregiver's sleep, and 6 questions assessing the child's sleep based on caregiver observation. Sleep diary items, either alone or in combination will serve as subjective measures of sleep quality, difficulty falling asleep, nighttime awakenings, and sleep duration. Sleep quality will be measured using an 11-point NRS (0 to 10) in which 0 indicates worst possible sleep while 10 indicates best possible sleep. The parents/caregivers will be instructed to complete the questions about the child's sleep upon awakening for the day.

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

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 6.1, Table 1 (Part A), and Table 2 (Part B).

The SCORAD assessment tool is provided in the investigator site binder.

NOTE: For the purpose of assessing the extent of disease (A), the proportion assigned to different body regions is different in children <2 years of age, as compared to older children. Refer to the SCORAD assessment tool in the investigator site binder for details.

6.2.2.16. Atopic Dermatitis Area Photographs

At select study sites in part B, photographs will be taken of a representative area(s) of AD involvement (eg, the lesional area(s) used for SCORAD assessments on day 1/baseline [predose]). Subsequent photographs of the same area(s) will be taken at time points according to Section 6.1, Table 2 (Part B).

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

6.2.2.17. Topical Corticosteroids Accountability

In part B, at every in-clinic visit following the baseline visit, the type, amount, 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, caregivers will be asked to record TCS use daily, from start of 2-week TCS standardization period on day -14 through the end of the study, on an e-diary:

- Use of TCS (yes/no)
- Why did you not apply the topical corticosteroid to your child today?

6.2.2.18. Pediatric Asthma Symptom Questionnaire

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

The questionnaire will be completed only for the subset of patients with ongoing asthma. It is to be completed by the child's parent or caregiver who fluently speak a language in which the questionnaire is presented, at time points according to Section 6.1, Table 2 (Part B). It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study.

The PASQ is provided in the investigator site binder.

6.2.3.6. Ophthalmological Examinations (Part B only)

Patients who have history of certain eye disorders (conjunctivitis, blepharitis or keratitis) within 12 months prior to the screening visit will be referred to an ophthalmologist (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 AESIs related to eye disorders (refer to Section 7.2.3) 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. An ophthalmology examination form will be provided to patients by the site, which they will carry to the ophthalmologist on the day of examination. This form will be completed by the ophthalmologist and this information will be transcribed into the study CRFs. Appropriate treatment for these AEs will be prescribed by the ophthalmologist. The investigator may also have a conversation with the ophthalmologist to discuss the further course of action for these patients.

6.2.4. Pharmacokinetic and Antibody Procedures

6.2.4.1. Drug Concentration Measurements and Samples

Serum samples for measuring functional dupilumab concentrations will be collected at time points listed in Section 6.1, Table 1 (Part A), and Table 2 (Part B).

6.2.4.2. Immunogenicity Measurements and Samples

Serum samples for ADA assessment will be collected at time points listed in Section 6.1, Table 1 (Part A) and Table 2 (Part B). Samples positive in the ADA assay will be analyzed for the presence of neutralizing antibody in the NAb assay.

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 OLE study may be considered based on the overall clinical presentation at that time. Patients who are considered for follow-up may be asked to return to the clinic to have additional samples collected for analysis.

6.2.5. Biomarker Procedures

Thymus and activation-regulated chemokine and total serum IgE are markers of Th2 activity as downstream mediators in the IL-4/IL-13 signaling pathway (Wirnsberger 2006, Takeda 1997). These analytes will be assessed as measures of 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 (LDH) levels have also been shown to correlate with disease severity and activity in patients with AD (Mukai 1990).

6.2.7. Research Testing

6.2.7.1. Research Samples

Use and Storage of Research Samples (Serum)

Any unused serum samples collected for dupilumab concentrations or ADA measurements, may be used for exploratory biomarker research related to AD, inhibition of the IL-4Rα pathway with an antibody, treatment response (PD and or predictive), vaccine response, to investigate unexpected AEs, or to identify markers associated with adverse reactions.

6.2.7.2. Tape Stripping Sub-study - Optional

An optional tape stripping sub-study may be performed at a subset of study sites. The purpose of the tape stripping sub-study is to identify molecular changes associated with clinical or biomarker response to IL-4/13 pathway inhibition (via IL-4Rα blockade); to study AD and related diseases, prognosis and progression, predicators of treatment response, or other clinical outcome measures, as well as why some patients may respond better than others. Gene expression (by RNA sequencing and/or other methods) analyses will be performed on tape stripping samples. Results from these exploratory analyses will not be included in the clinical study report.

Parents or legal guardians who agree for their child to participate in the optional tape stripping sub-study will be required to sign a separate sub-study ICF before collection of the samples. Baseline samples should be collected on day 1/baseline (pre-dose). A second sample will be collected at week 16 to assess treatment effects. Patients are not required to participate in the tape stripping sub-study to enroll in the primary study.

6.2.7.3. Genomics Sub-study - Optional

The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to IL-4/13 pathway inhibition (via IL-4Rα blockade), atopic disease risk, prognosis and progression, or other clinical outcome measures. These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease.

Parents or legal guardians who agree for their child to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. DNA cheek swab samples should be collected on day 1/baseline (pre-dose) but may be collected at any study visit. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA samples for the genomics sub-study were double-coded during part A and will be single-coded during part B as defined by the ICH guideline E15. Sub-study samples may be stored for up to 15 years after the final date of the clinical study report and may be used for research purposes. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Genome-wide studies, including (but not limited to) single nucleotide polymorphism analyses, genomic sequencing, and transcriptome sequencing may also be performed. If indicated, genomic analyses may also be performed to identify markers associated with toxicity.

9.3.2. Safety Analysis Set

For part A, the safety analysis set (SAF) includes all patients who received any study drug in part A; it is based on the treatment received (as treated). Both safety and efficacy variables for part A will be analyzed using the SAF.

For part B, the SAF includes all randomized patients who received any study drug in part B.

Treatment compliance/administration and all clinical safety variables in parts A and B will be analyzed using the SAF, as treated.

9.3.3. Pharmacokinetic Analysis Sets

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

The PK analysis set will be defined in parts A and B separately.

9.3.4. Immunogenicity Analysis Sets

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

The neutralizing antibody (NAb) analysis set includes all patients who received any study drug and had at least 1 non-missing result in the NAb assay (patients who are ADA negative will be set to negative in the NAb analysis set).

The ADA and NAb analysis sets will be defined in parts A and B separately.

9.4. Patient Disposition

The following will be provided for parts A and B separately:

- The total number of screened patients
- The total number of enrolled patients in part A
- The total number of randomized patients in part B
- The total number of patients in each analysis set (eg, FAS, provided in Section 9.3)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- 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
- The total number of patients who completed the study treatment and discontinued the study treatment with reasons for discontinuation

9.5.3.3. Treatment Exposure

The duration of exposure in part A is 7 days.

The duration of exposure in part B will be presented by treatment group and calculated as:

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

The number and percentage of patients exposed to study drug will be presented by specific time periods for each dose 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 dose group using number of patients, means, standard deviation (SD), minimums, medians, and maximums.

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

9.5.3.4. Treatment Compliance

Compliance with study treatment will be calculated separately for parts A and B as follows:

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

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

9.5.4. Analysis of Drug Concentration Data

No formal statistical analysis will be performed in parts A and B. Functional dupilumab concentration in serum will be summarized at each time point using descriptive statistics. In part A, PK parameters will be derived using non-compartmental analysis (NCA) and summarized by treatment and age group. The data may be combined with data from other pediatric studies for analysis using population methods. Any population PK analysis will be reported separately.

9.5.5. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA and NAb responses observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative or missing
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 4-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

Table 2: Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B)

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

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

For part B of the study, a sample size of approximately 160 patients is planned. Randomization will be stratified by baseline weight (≥5-<15 kg and ≥15 to <30 kg), baseline disease severity (IGA=3, 4), and region/country (North America, Europe, Japan, and China). To ensure adequate representation of patients from Japan and China, randomization slots will be reserved for patients from these countries in an interactive web response system (IWRS). The number of patients with moderate AD (IGA=3) will be capped at approximately 40.

4.2. Study Population

The study population includes pediatric patients (aged ≥6 months to <6 years at the time of screening visit) who have severe AD (part A) or moderate-to-severe AD (part B) that cannot be adequately controlled with topical AD medications.

4.2.1. Inclusion Criteria

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

1. Male or female ≥6 months to <6 years of age at the screening visit
2. Diagnosis of AD according to the American Academy of Dermatology consensus criteria at the screening visit
3. Patients with documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s)

NOTE:

- Patients who are unable to achieve and/or maintain remission and low disease activity (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of medium to higher potency TCS (±TCI as appropriate), applied for at least 28 days of use, or for the maximum duration recommended by the product prescribing information, whichever is shorter, will meet the definition of inadequate response for the purpose of this study.
- 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 (±TCI as appropriate*), applied for at least 28 days during the screening period or for the maximum duration recommended by the product prescribing information, whichever is shorter. Patients who demonstrate inadequate response, as defined above, or develop important side effects (eg, significant skin atrophy, systemic effects) during this period will still be eligible for inclusion in the study.