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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 2/3 STUDY INVESTIGATING THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF DUPILUMAB IN PATIENTS AGED ≥6 MONTHS TO <6 YEARS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Compound:	Dupilumab
Study Name:	Liberty AD PRESCHOOL
Clinical Phase:	2/3
Protocol Number:	R668-AD-1539
Protocol Version:	R668-AD-1539 Amendment 4
Amendment 4 Date of Issue:	See appended electronic signature page for approval date
Amendment 3 Date of Issue:	22 Nov 2019
Amendment 2 Date of Issue:	05 Jul 2017
Amendment 1 UK Date of Issue:	31 March 2017
Original Date of Issue:	19 Dec 2016
Scientific/Medical Monitor:	[redacted]

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AMENDMENT HISTORY

Amendment 4

Amendment 4 consists of a non-substantial change only. Changes to protocol and affected sections are summarized below.

Change	Sections Changed
The number of patients with moderate AD (IGA=3) will be capped at approximately 40 in order to meet the European Union (EU) regulatory requirement (as per commitment in the approved Pediatric Investigational Plan) to enroll approximately 120 patients with severe AD (IGA=4).	Study Synopsis: Study Design Study Synopsis: Population Section 3 Study Design Section 4.1 Number of Patients Planned Section 5.5 Method of Treatment Assignment

Amendment 3

Protocol amendment 3 is a substantial amendment seeking approval of the dose regimens for part B of the study. This amendment will be submitted to the Regulatory Authorities prior to the start of dosing in part B. Changes to protocol and affected sections are summarized below.

Change	Sections Changed
Based on data from part A and PK simulations, as well as data from study R668-AD-1652, dose regimens were added to the protocol for part B of study. In part B, patients (≥6 mos-<6 yrs) will be randomized to receive either placebo or dupilumab (200 mg for patients ≥5-<15 kg or 300 mg for patients ≥15-<30 kg) every 4 weeks (Q4W). Randomization stratification in part B was changed from by age group and region to by body weight, baseline disease severity, and region/country. PK data from part A and from other completed dupilumab studies have shown that weight rather than age is the most important covariate that determines exposure. Accordingly, a weight-tiered fixed-dose regimen was chosen for part B. Randomization stratified by weight will enable patients to receive correct dose for weight category and normalize exposure across weight ranges. Study drug treatment will be administered by study site personnel during part B. Added description of how blinding will be maintained during part B.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Population Clinical Study Protocol Synopsis: Treatments Clinical Study Protocol Synopsis: Statistical Plan Section 1.2.1 Rationale for Study Design Section 1.2.2 Rationale for Dose Selection Figure 1 Randomization Scheme (Part B) Section 3.1 Study Description and Duration Section 4.1 Number of Patients Planned Section 5 Study Treatments Section 5.1 Investigational and Reference Treatments Section 5.5 Method of Treatment Assignment Table 2 Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B), footnote 9. Section 9.1 Statistical Hypothesis Section 9.2 Justification of Sample Size Section 9.5.2.1 Primary Efficacy Analysis
The target population with respect to disease severity was changed from severe AD to moderate-to-severe AD for part B. In initial interactions with a Competent Authority which were held at a time when there was no data on the use of dupilumab in the pediatric population, the sponsor was advised to limit the patient population to severe patients. 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. Accordingly, the sponsor was recently advised to broaden the patient population to moderate-to-severe disease by a Competent Authority. This will maximize the number of patients that will benefit from this drug and facilitate enrollment in study.	Title Clinical Study Protocol Synopsis: Objectives Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Population Section 1.2.1 Rationale for Study Design Section 2.1 Primary Objective Section 2.2 Secondary Objectives Section 3.1 Study Description and Duration Section 4.2 Study Population Section 4.2.1 Inclusion Criteria #4, 5, and 6
Added 2-week TCS standardization period using low potency TCS to part B of this study. The screening period must not exceed 56 days	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Treatments

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Change	Sections Changed
(including TCS standardization). TCS standardization ensures only patients with inadequate response to TCS are enrolled as patients who respond will be considered screen failures at the baseline visit. This will enable a more accurate estimate of the true treatment effect of dupilumab. Use of medium potency steroids was changed to low potency steroids as required during the study. This age group is particularly vulnerable to the systemic side effects of TCS such as hypothalamic pituitary axis suppression due to increased systemic absorption resulting from a higher surface area to body weight ratio as compared to older children and adults. Use of low potency TCS is expected to mitigate this risk and maximize patient safety. Clarified use of background and rescue treatments during the study, including treatments permitted and prohibited. Specified rescue treatment only allowed after day 14 in part B. This ensures investigators give study drug adequate time for onset of effect before resorting to other available medications of rescue. As patients who are rescued are considered non-responders, this will enable an accurate assessment of treatment effect of the study drug. Medium potency TCS has been added as rescue treatment. In previous versions of this protocol, patients were required to have moisturizers applied at least twice daily during the 7 consecutive days prior to randomization (14/14 total applications) and during study. This criterion was relaxed to require at least 11/14 total applications prior to randomization for patient to be eligible. This change was based on feedback from investigators that the previous criterion was felt to be overly stringent in a pediatric population. Corrected post-randomization duration of application of moisturizers for part B to 28 weeks. A pre-specified algorithm will be used to classify rescue treatment for responder analysis. A blinded review of post-baseline medications will be done to adjudicate rescue treatment.	Section 1.2.1 Rationale for Study Design Section 3.1 Study Description and Duration Section 4.2.1 Inclusion Criteria #3 and #7 Section 4.2.2 Exclusion Criteria #3 and #7 (previously #4 and #8) Figure 3 Study Flow Diagram (Part B) Section 5 Study Treatments Section 5.2 Background Treatments Section 5.3 Rescue Treatments Section 5.4.2.1 Reasons for Permanent Discontinuation of Study Drug Table 2 Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B) Section 6.2.2.17 Topical Corticosteroids Accountability Appendix 2 Permitted and Prohibited Steroid Medication
Increased the duration of screening period for part B from a maximum of 35 days to a maximum of 56 days. This change was implemented to	Clinical Study Protocol Synopsis: Study Design Section 3.1 Study Description and Duration

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Change	Sections Changed
allow patients/caregivers more flexibility to complete all screening procedures to be eligible for randomization. Specifically, given the age group being studied, it is expected that a substantial proportion of patients would need a course of treatment with medium potency TCS for 4 weeks during screening period to demonstrate inadequate response, and hence meet inclusion criterion 3 (Patients with documented recent history of inadequate response to topical AD medication(s))	Section 4.2.1 Inclusion Criteria #3 and #10 Figure 3 Study Flow Diagram (Part B) Section 5.7.1 Prohibited Medications and Procedures Table 2 Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B)
Added other (exploratory) objectives to assess effects of dupilumab on blood and skin biomarkers and to study its mechanism of action (related to efficacy and/or safety), why some patients respond better (safety and/or efficacy), and interleukin (IL)-4 receptor pathway, and AD and related diseases.	Clinical Study Protocol Synopsis: Objectives Section 2.3 Other Objectives
Japan and China added as participating countries for part B. 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. This study will provide data for regulatory approval and labeling in Japan and China.	Clinical Study Protocol Synopsis: Site Locations Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Sample Size Section 3.1 Study Description and Duration Section 4.1 Number of Patients Planned Section 5.5 Method of Treatment Assignment Section 13.1 Good Clinical Practice Statement
Added that patients may be rescreened twice in part B if they have transient intercurrent events such as an active acute infection or need for vaccination which disqualifies them from an initial successful screening visit. Many pediatric patients have transient incidental conditions like systemic infections and recent vaccinations. The option for rescreening twice will allow such patients to be enrolled once these transient conditions have resolved, thus maximizing clinical benefit.	Section 3.1 Study Description and Duration
Clarified patient eligibility for the open-label extension (OLE) study. Any patient screened for the OLE will not participate in the follow-up period of current study. Updated age range for OLE study, R668-AD-1434, based on a protocol amendment for that study.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Study Duration Section 1.1 Introduction Section 1.2.1 Rationale for Study Design Section 3.1 Study Description and Duration Section 5.8 Continuation of Dupilumab Treatment in an Open-Label Extension Study Section 9.5.3.1 Adverse Events

Change	Sections Changed
Noted that dupilumab has been approved for marketing in the US, EU, and Japan for treatment of moderate-to-severe AD in adults and adolescents. Updated background information based on results of previous studies. New sections were added to discuss the risks/benefits from previous studies.	Section 1.1 Introduction Section 1.2.1 Rationale for Study Design Section 1.2.3 Risks/Benefits of Participating in Study(new) Section 1.2.3.1 Benefits (new) Section 1.2.3.2 Risks (new) Section 1.2.3.3 Risk/Benefit Conclusion (new)
Updated planned sample size to 160 patients (80 patients per group) from 240 (80 patients per group). The previous study design assumed 3 treatment groups (2 dupilumab and 1 placebo) while the current design includes 2 treatment groups (1 dupilumab and 1 placebo). Revised power calculations based on new data from pediatric studies with dupilumab. The revised power calculations were based on data from the phase 3 TCS combination study in children (≥6 to <12 years) with severe AD (R668-AD-1652) and additional justification from the phase 3 TCS combination study in adults with moderate-to-severe AD (R668-AD-1224). Additional support was also provided by the phase 3 monotherapy study in adolescents with moderate-to-severe AD (R668-AD-1526).	Clinical Study Protocol Synopsis: Population Clinical Study Protocol Synopsis: Statistical Plan Section 3.1 Study Description and Duration Section 4.1 Number of Patients Planned Section 5.5 Method of Treatment Assignment Section 9.2 Justification of Sample Size
Added assessment of neutralizing antibodies (NAbs). This will be done on samples collected for ADA assessment.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Procedures and Assessments Clinical Study Protocol Synopsis: Statistical Plan Section 8.4 Immunogenicity Variables (previously Anti-drug Variables) Section 9.3.4 Immunogenicity Analysis Sets (new) Section 9.5.5 Analysis of Immunogenicity Data (previously Analysis of Anti-drug Antibody Data)

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Change	Sections Changed
An optional tape stripping sub-study at selected study sites was added to the protocol. Samples collected may be used for exploratory biomarker analysis.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Procedures and Assessments Section 3.1 Study Description and Duration Table 2 Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B) Section 6.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 6.2.7.2 Tape Stripping Sub-study - Optional Section 9.5.6 Analysis of Biomarker Data
Added collection of assent from patients, as applicable, per local regulatory guidelines	Clinical Study Protocol Synopsis: Study Design Section 3.1 Study Description and Duration Section 4.2.1 Inclusion Criteria #8 Table 2 Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B), footnotes Section 6.2.1 Procedures Performed Only at the Screening/Baseline Visit
Added inclusion criterion #10 for a weekly average worst scratch/itch score ≥4 at baseline (part B) to ensure that patients have a certain minimum intensity of pruritus at baseline so that a treatment effect can be detected. Added inclusion criterion #11 for application of low potency TCS for at least 11 days during TCS standardization period (part B). This is to ensure only patients adequately compliant with TCS application are enrolled.	Section 4.2.1 Inclusion Criteria #10 and #11 (new)
Revised exclusion criterion #1 to exclude patients who received prior treatment with dupilumab to prevent any confounding of treatment effect resulting from past use.	Section 4.2.2 Exclusion Criteria #1
Revised exclusion criterion #2 to exclude patients with history of important side effects of low potency TCS. Deleted previous exclusion criterion #3 which excluded patients with ≥30% of the total lesional surface located on areas of thin skin that cannot be safely treated with medium potency TCS. These changes followed the change in background therapy from medium potency to low potency TCS.	Section 4.2.2 Exclusion Criteria #2 and previous exclusion criterion #3

Change	Sections Changed
Clarified live (attenuated) vaccines are prohibited, but inactivated vaccines are permitted. Clarified timing of sample collection for vaccine sub-study. Added provision patients may be offered re-vaccination during the OLE in case of inadequate response to vaccines administered during study. The Vaccination Record Form was removed from protocol appendices as form and process described was not consistent with actual process.	Section 4.2.2 Exclusion Criteria #8 (previously #9) Section 5.7.1 Prohibited Medications and Procedures Section 6.2.6 Vaccine Response – Optional Appendix Vaccine Record Form (deleted)
Specified that tuberculosis testing will be performed according to local guidelines.	Section 4.2.2 Exclusion Criteria #17 (previously #18)
Added exclusion criterion #27 for patients with body weight <5 kg or ≥30 kg at baseline (part B only). Patients <5 kg excluded to prevent risks to patient safety due to exposure to study drug at levels that are higher than what have been studied in previous dupilumab studies in adults and pediatric patients. Patients ≥30 kg excluded due to potential reduced efficacy from under exposure to study drug.	Section 4.2.2 Exclusion Criteria #27 (new)
Moved text regarding replacement of patients from Section 5.4.2 to Section 4.4 for appropriate placement. Clarified study drug discontinuation criteria only applicable to part B.	Section 4.4 Replacement of Patients Section 5.4.2 Study Drug Discontinuation
Specified that study drug will be temporarily discontinued in the event of serum creatinine >1.5×ULN	Section 5.4.2.2 Reasons for Temporary Discontinuation of Study Drug
Removed tanning in a bed/booth from list of prohibited concomitant procedures	Section 5.7.1 Prohibited Medications and Procedures
Made adjustment to or clarified some existing assessments and added assessments based on feedback from investigators and experience gained from conduct of part A of this study. Made corresponding changes to assessments/ footnotes in schedule of events for part B.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Procedures and Assessments Section 3.1 Study Description and Duration Table 2 Schedule of Events (Part B) Section 6.1.2 Unscheduled Visits Section 6.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 6.2.2 Efficacy Procedures Section 6.2.2.1 Assessment of Pruritus Section 6.2.2.2 Assessment of Skin Pain Section 6.2.2.3 Assessment of Sleep Quality and Other Sleep-Related Concepts Using Sleep Diary

Change	Sections Changed
	Section 6.2.2.4 Caregiver Global Impression of Disease Section 6.2.2.5 Caregiver Global Impression of Change Section 6.2.2.8 Infants' Dermatology Quality of Life Index Section 6.2.2.9 Dermatitis Family Index Section 6.2.2.11 Investigator Global Assessment Section 6.2.2.17 Topical Corticosteroids Accountability Section 6.2.2.18 Patient Asthma Control Questionnaire Section 6.2.2.19 Caregiver-Reported Nasal Symptom Questionnaire Section 6.2.3.6 Ophthalmological Examination (Part B Only) Section 6.2.3.1 Vital Signs Section 6.2.4.2 Immunogenicity Measurements and Samples Section 6.2.5 Biomarker Procedures Section 6.2.7.1 Research Samples
For consistency with criterion for temporary discontinuation of study drug, creatine phosphokinase (CPK) isoenzymes will be measured when CPK >2.5× upper limit of normal (ULN) (previously >5× ULN)	Section 6.2.3.5 Laboratory Testing
To be consistent with current practice DNA samples will be single-coded in part B instead of double-coded as done in part A.	Section 6.2.7.3 Genomics Sub-study - Optional

Change	Sections Changed
Described how major protocol violations will be determined. Renamed first-step (1-step) analysis as primary analysis. If performed, it will be the final analysis for primary and secondary efficacy endpoints. Further described analyses that may be performed, including multiple imputation method. Added hierarchical procedure to be used for part B to control overall Type-1 error rate. Added details on Immunogenicity analysis.	Clinical Study Protocol Synopsis: Statistical Plan Section 3.2 Planned Interim Analysis Section 9.3.1 Efficacy Analysis Sets Section 9.5.2.1 Primary Efficacy Analysis Section 9.5.2.2 Secondary Efficacy Analysis Section 9.5.2.3 Multiplicity Considerations Table 3 Preliminary Statistical Hierarchy for Multiplicity Control Section 9.5.2.4 Primary Analysis of the Study Section 9.5.3.1 Adverse Events Section 9.5.3.2 Other Safety Section 9.5.3.3 Treatment Exposure Section 9.5.5 Analysis of Immunogenicity Data
Clarified/updated list of adverse events of special interest (AESIs) including addition of clinically symptomatic eosinophilia and removal of malignancy. Also, specified that any patient with an AESI related to an eye disorder will be referred to an ophthalmologist (per health authority request).	Section 7.2.3 Other Events that Require Accelerated Reporting, Adverse Events of Interest
Clarified definition of serious adverse event related to hospitalization. Revised definitions of adverse event severity (mild, moderate, and severe) for the younger pediatric population in this study.	Section 7.1.2 Serious Adverse Event Section 7.3.1 Evaluation of Severity
Specified a new key secondary endpoint for pruritus and added other secondary endpoints for worst scratch/itch NRS, skin pain NRS, and sleep quality NRS scores, and improvement in worst scratch/itch NRS score ≥4 and ≥3.	Clinical Study Protocol Synopsis: Endpoints Section 8.2.2 Secondary Endpoints
Modified descriptions of PK variables and definition of PK analysis set.	Section 8.3 Pharmacokinetic Variables Section 9.3.3 Pharmacokinetic Analysis Set (previously Other Analysis Sets)
Edits/Clarifications/Updates Editorial changes were made throughout protocol for further clarification, consistency, and completeness, and, if appropriate, correction. All references to the study reference manual or study manual have been replaced with investigator site binder.	Various

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Amendment 2

The changes to the protocol and the affected sections are highlighted below.

* Changes noted with an "*" were included in Protocol Amendment R668-AD-1539.01UK approved on 31 March 2017 and were reviewed and approved by the MRHA. However, the sponsor is incorporating these changes globally into one amendment, titled "R668 AD 1539 Amendment 2" to harmonize the protocol across regions and to simplify regulatory submissions.

Change	Sections Changed
Increased the follow-up period for patients who decline or are not eligible for a subsequent OLE study, from 4 weeks to 8 weeks. This change has been implemented to comply with a request from a competent authority. This change will ensure a sufficient follow-up period for patients who decline or are ineligible for enrollment into OLE at week 4 and hence maximize patient safety.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Study Duration Section 3.1 Study Description and Duration Figure 2 Study Flow Diagram (Part A) Section 3.1.2 Dose Escalation and Study Stopping Rules (Figure 4) Section 5.8 Continuation of Dupilumab Treatment in an Open-Label Extension Study Table 1 Schedule of Events for Screening, Single-Dose Treatment and PK Sampling Period (Part A)
Added an ADA assessment at day 8 (part A) based upon request from health authority	Table 1 Schedule of Events for Screening, Single-Dose Treatment and PK Sampling Period (Part A)
The study day at Week 24 was corrected to day 169 (listed incorrectly previously as day 141).	Table 2 Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B)
*Per request from a competent authority, stated that a substantial amendment (with supporting pharmacokinetic data) seeking approval of the part B doses will be submitted to the Regulatory Authorities prior to dosing in part B.	Clinical Study Protocol Synopsis: Study Design Section 1.2.2 Rationale for Dose Selection Section 3.1 Study Description and Duration
*Per request from a competent authority, clarified that an amendment to the ongoing open-label extension (OLE) study (R668-AD-1434) will be submitted to the Regulatory Authorities for approval to allow patients aged 6 months to <6 years who participate in this study (R668-AD-1539) to enroll into the OLE.	Clinical Study Protocol Synopsis: Study Design Section 3.1 Study Description and Duration
*Per request from a competent authority, changed wording of the criterion for when dose escalation to the next cohort will not immediately proceed (removed "similar" before "severe AE").	Section 3.1.2 Dose Escalation and Study Stopping Rules
*Per request from a competent authority, added end of study section and definition.	Section 3.1.3 End of Study Definition

Change	Sections Changed
Added the following exclusion criteria: "Treatment with crisaborole within 2 weeks prior to the baseline visit." This exclusion criterion has been added to minimize any carry-over effects into the treatment period. This will minimize any confounding of efficacy assessments for the study drug.	Section 4.2.2 Exclusion Criteria #8
Clarified the text indicating where moisturizers should be applied by the deletion of the following text in the third sentence "on the are(s) of nonlesional skin designated for such assessments"	Section 5.2 Background treatment(s)
Added text that stated "Investigators may also consider rescue with crisaborole. Rescue treatment for these topical therapies should be used as per prescribing information and local guidelines."	Section 5.3 Rescue Treatment (s)
Updated the text regarding replacement of who prematurely withdrawal from part A of the study.	Section 5.4.2 Study Drug Discontinuation
Changed "dupilumab" to "study drug" in the sentence "Anaphylactic reaction or other severe systemic reaction to study medication"	Section 5.4.2.1 Reasons for Permanent Discontinuation of Study Drug
Removed reference to the interactive IVRS (interactive voice response system) since the IWRS (interactive web response system) system is the only one used.	Section 5.5 Method of Treatment Assignment Section 10.2 Electronic Systems
Added 1 medication to the list of prohibited agents Treatment with crisaborole (only for part B). Crisaborole has been added to the list of prohibited medications to prevent any confounding of efficacy assessments. Permitting use of crisaborole would have allowed patients to substitute crisaborole for TCS, thus preventing an accurate assessment of steroid sparing effect of the study drug. Moreover, crisaborole is only approved for patients with moderate to severe AD, and the target patient population will have severe disease at baseline.	Section 5.7.1 Prohibited Medications
*Changed conditions for potential entry into the OLE (R668-AD-1434) so that all patients in part B will be able to roll over into the OLE at the end of the treatment period.	Section 5.8 Continuation of Dupilumab Treatment in an Open-Label Extension Study
Clarified wording for research samples, because only serum is being collected	Table 2 Schedule of Events for the Screening, Treatment, and Follow-Up Period (Part B) Section 6.2.7.1 Research Samples

Change	Sections Changed
Added a copy of the Investigator Global Assessment (IGA) scale to Appendix 4 and cross-referenced the IGA in this section.	Section 6.2.2.5 Investigator Global Assessment
Added an Ophthalmological Examination section: Patients who have history of certain eye disorders (conjunctivitis, blepharitis or keratitis) will be referred to an ophthalmologist (preferably with expertise in treating pediatric patients or Cornea and External Eye Disease ['front-of-the-eye'] subspecialty expert). Any baseline findings will be documented as part of the patient's medical history and/or physical exam, as appropriate. Patients who experience adverse events of special interest related to eye disorders (refer to Section 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. Certain types of eye disorders (conjunctivitis, blepharitis, keratitis) are an adverse event of special interest for the study drug. Including referral to a specialist will allow a more robust and comprehensive evaluation of baseline disease status of patients with history of these disorders, as well as of any treatment emergent adverse events falling under this category.	Section 6.2.3.6 Ophthalmological Examination (Part B Only)
Clarified wording for vaccine response assessment, to allow more flexibility in timing Patients who do not get an adequate response to vaccine administration during part B of the study may be offered re-vaccination. The details about re-vaccination procedure will be provided in a protocol amendment prior to the start of part B.	Section 6.2.6 Vaccine Response - Optional
Revised storage duration for DNA samples, to be consistent with the current practice	Section 6.2.7.3 Genomics Sub-study - Optional
The list of AESIs has been revised across the dupilumab program in AD and incorporates the data gathered from adult phase 3 studies, the dupilumab risk profile, and regulatory feedback. This will enable focus of pharmacovigilance activities on identified and potential risks with this drug.	Section 7.2.3 Other Events that Require Accelerated Reporting

Change	Sections Changed
The investigator will also assess whether the AES are related to any study procedures (as listed in Tables 1 and 2).	Section 7.3.2 Evaluation of Causality
Removed identification of patients by their initials due to privacy laws in some countries	Section 13.3 Patient Confidentiality and Data Protection
Made editorial changes/corrections	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Endpoints, Primary Clinical Study Protocol Synopsis: Endpoints, Secondary Figure 3 Study Flow Diagram (Part B) Table 1 Schedule of Events for Screening, Single-Dose Treatment and PK Sampling Period (Part A) Section 8.2.1 Primary Endpoints Section 8.2.2 Secondary Endpoints

Amendment 1 UK

The purpose of this amendment is to address a number of requests for revision of the protocol from the Medicines and Healthcare Products Regulatory Agency in the United Kingdom.

The changes to the protocol and the affected sections are highlighted below.

Change	Sections Changed
Clarified that an amendment to the ongoing open-label extension (OLE) study (R668-AD-1434) will be submitted to the Regulatory Authorities for approval to allow patients aged 6 months to <6 years who participate in this study (R668-AD-1539) to enroll into the OLE.	Clinical Study Protocol Synopsis: Study Design Section 3.1 Study Description and Duration
Stated that a substantial amendment (with supporting pharmacokinetic data) seeking approval of the part B doses will be submitted to the Regulatory Authorities prior to dosing in part B.	Clinical Study Protocol Synopsis: Study Design Section 1.2.2 Rationale for Dose Selection Section 3.1 Study Description and Duration
Changed wording of the criterion for when dose escalation to the next cohort will not immediately proceed.	Section 3.1.2 Dose Escalation and Study Stopping Rules
Added end of study section and definition.	Section 3.1.3 End of Study Definition
Changed conditions for potential entry into the OLE (R668-AD-1434) so that all patients in Part B will be able to roll over into the OLE at the end of the treatment period.	Section 5.8 Continuation of Dupilumab Treatment in an Open-Label Extension Study

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2/3 Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab In Patients Aged ≥6 Months to <6 Years With Moderate-to-Severe Atopic Dermatitis
Site Locations **Principal Investigator**	Multiple sites in North America, Europe, Japan, and China.
Objectives	**Primary Objectives** The primary objective for part A of the study is to characterize the safety and pharmacokinetics (PK) of dupilumab administered as a single dose in pediatric patients, 6 months to less than 6 years of age with severe atopic dermatitis (AD). The primary objective for part B of the study is to demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with topical corticosteroids (TCS) in pediatric patients, 6 months to less than 6 years of age, with moderate-to-severe AD. **Secondary Objectives** The secondary objective of part A of the study is to evaluate the efficacy and immunogenicity of a single dose of dupilumab in patients 6 months to less than 6 years of age with severe AD. The secondary objective of part B is to assess the safety and immunogenicity of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in patients 6 months to less than 6 years of age with moderate-to-severe AD. **Other Objectives (Part B)** To assess the concentrations of dupilumab in serum following repeated subcutaneous (SC) dosing. To assess the effects of dupilumab on blood and skin biomarkers of inflammation in comparison with placebo. To study dupilumab's mechanism of action (related to efficacy and/or safety), why some patients respond better than others (safety and/or efficacy), type 2 inflammation, as well as AD and related diseases.

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

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.

	Patient participation in the genomics sub-study in parts A and B is optional. Samples for DNA analysis will be collected from patients whose parents or legal guardians agree to enroll them in the optional sub-study and sign a separate genomics sub-study informed consent form (ICF). Patient participation in the vaccination sub-study in part B is optional. Patients' parents or legal guardians who plan to have their children vaccinated during the study and agree to enroll them in the optional sub-study, will sign a separate vaccination sub-study ICF for the collection of 2 blood samples (one sample will be drawn before administration of the vaccine, and the second sample will be drawn 3 to 4 weeks [maximum 6 weeks] after administration of the vaccine) for assay of vaccine immunoglobulin G (IgG) in serum for each vaccine administered. Patient participation in a tape-stripping sub-study at selected study sites in part B is optional. Tape stripping samples may be taken for exploratory biomarker analysis from patients whose parent(s) or legal guardian(s) consent for the child to participate in this optional sub-study. An OLE study (R668-AD-1434) in patients aged 6 months to <18 years old is currently ongoing. Patients who complete the treatment period in either part A or part B may be eligible to enroll in this OLE study in which they will receive treatment with dupilumab.
Study Duration	The duration of the study for a patient in part A is approximately 8 weeks, excluding the screening period (patients would have the option to enroll into an OLE study at week 4), and duration of the study for a patient in part B is approximately 28 weeks, excluding the screening period (patients would have the option to enroll into an OLE study at week 16). A patient cannot participate in both parts A and B of the study.
Population **Sample Size:**	For part A, approximately 40 pediatric AD patients aged ≥6 months to <6 years are planned to be enrolled in 4 cohorts as follows: • 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 To ensure adequate representation of patients from all age-groups, a cap will be placed on the number of patients who 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 For part B, approximately 160 pediatric AD patients aged ≥6 months to <6 years are planned to be randomized. Randomization will be stratified by baseline weight (≥5 to <15 kg or ≥15 to <30 kg), by baseline disease severity (IGA=3, 4), and by region/country (North America, Europe, Japan, and China) in a 1:1 ratio to dupilumab or placebo. 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. The number of patients with moderate AD (IGA=3) will be capped at approximately 40. The dose regimens are dupilumab Q4W tiered fixed-dose regimen (200 mg or 300 mg) or placebo Q4W.
Target Population:	The study population includes pediatric patients with severe AD (part A) or moderate-to-severe AD (part B) aged ≥6 months to <6 years that cannot be adequately controlled with topical AD medications.
Treatments	Study treatment is administered by study site personnel. Background and rescue treatment are to be applied by the patient's caregiver.
Study Drug Dose/Route/Schedule:	For part A, dupilumab SC, 3 mg/kg for dose cohorts 1A and 2A, and 6 mg/kg for dose cohorts 1B and 2B, given as a single dose on day 1. For part B, dupilumab is supplied in prefilled syringes for SC administration. • Patients with a baseline weight of ≥5 kg to <15 kg will receive dupilumab 200 mg SC on day 1 followed by the same dose given SC Q4W through week 12. • Patients with a baseline weight of ≥15 kg to <30 kg will receive dupilumab 300 mg SC on day 1 followed by the same dose given SC Q4W through week 12.
Placebo Route/Schedule:	For part B, 2 matching placebo formulations (without addition of active substance) will be used during the study: • placebo matching 200 mg dupilumab formulation • placebo matching 300 mg dupilumab formulation Patients in the ≥5 to <15 kg weight stratum will receive placebo-matching dupilumab 200 mg SC on day 1 and then Q4W through week 12. Patients in the ≥15 to <30 kg weight stratum will receive placebo-matching 300 mg Q4W through week 12.

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Background Treatment Dose/Route/Schedule:	Background treatment is applied by the patient's caregiver. For part B, patients are required to have moisturizers (emollients) applied at least twice daily for at least the 7 consecutive days immediately before randomization (not including the day of randomization). At least 11 of the 14 total applications must be applied for the subject to remain eligible for the study. Patients are to continue to have moisturizers applied throughout the remainder of the study (all 28 weeks where applicable). However, to allow adequate assessment of skin dryness, moisturizers should not be applied for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study. Patients may continue using stable doses of such moisturizers if initiated before the screening visit. For part B, starting on day -14, all patients are required to initiate treatment with low potency TCS using a standardized regimen according to protocol-specified guidelines. A list of steroids that can be used during the study will be provided to the investigators as part of the investigator site binder. Based on investigator discretion, low/mild potency TCS may also be used on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc).
Rescue Treatment Dose/Route/Schedule:	For parts A and B, medium or high potency TCS, systemic corticosteroids or nonsteroidal immunosuppressants, or TCI may be provided as rescue treatment to study patients at the discretion of the investigator. The use of rescue treatment is only allowed after day 14 of the study in part B. Investigators will be required to perform an Investigator Global Assessment (IGA) prior to starting rescue treatment and will initiate rescue treatment only in patients who either have an IGA score = 4 or have intolerable symptoms.
Endpoints	
Primary:	The primary endpoints in part A 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 is the 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 (**only in European Union [EU] and EU Reference Market Countries**): • Proportion of patients with Eczema Area and Severity Index (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

Secondary:	The secondary endpoints in part A are: • The incidence of serious adverse events (SAEs) and severe TEAEs to week 4 • Percent change in EASI score from baseline to week 4 • Percent change in SCORing Atopic Dermatitis (SCORAD) 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 the protocol. 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 numeric rating scale (NRS) score
Procedures and Assessments	Safety and tolerability will be assessed by vital signs, physical examinations, clinical laboratory tests, and clinical evaluations. Parents/caregivers will be asked to monitor all adverse events (AEs) experienced from the time of informed consent until their last study visit. Serum samples will be collected for assay of dupilumab concentrations, and PK parameters will be calculated using the dupilumab concentration data. Serum samples will be collected for ADA and NAb assessments and biomarker analyses, and research testing. Tape stripping samples (optional) may also be taken for exploratory biomarker analysis at a subset of study sites. Efficacy will be assessed during the study at specified clinic visits using the investigator-assessed IGA, EASI, SCORAD, and Body Surface Area (BSA) involvement, parent/caregiver-reported worst scratch/itch NRS, skin pain NRS, and parent/caregiver-reported measures of AD symptoms, sleep, and quality of life (QOL).

Statistical Plan	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 group), at the 2-sided 5% significance level, will provide: • 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 that the percentages are 69.7% and 26.8% for the dupilumab and placebo groups, respectively. The analyses for parts A and B will be performed separately. For parts A and B, demographic and baseline characteristics, safety, PK, ADA, and NAb data will be summarized descriptively by treatment group. For part A, the open-label portion of the study, descriptive statistics of the efficacy endpoints will be summarized. No statistical hypothesis will be tested. For part B, the efficacy analysis will be performed for the comparisons between the dupilumab treatment groups and the placebo group. Patients will be randomized in a 1:1 ratio, stratified by baseline weight, baseline disease severity, and region/country. No multiplicity adjustments will be made for part A. For part B, a hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint(s) and the secondary endpoints for the dupilumab dose regimen vs placebo. The abbreviated, preliminary plan for hierarchical testing order for the primary endpoint and key secondary endpoints are provided in the protocol. Details of the multiplicity adjustment will be provided in the statistical analysis plan (SAP).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-IL-4Rα	Anti-interleukin 4 receptor subunit alpha
AST	Aspartate aminotransferase
BL	Baseline
BSA	Body surface area
BUN	Blood urea nitrogen
CDLQI	Childrens' Dermatology Life Quality Index
CGIC	Caregiver Global Impression of Change
CGID	Caregiver Global Impression of Disease
CL	Clearance
CLA	Cutaneous lymphocyte antigen
$C_{max,ss}$	Maximum concentrations at steady-state
CNSQ	Caregiver-Reported Nasal Symptom Questionnaire
C_{trough}	Lowest concentration in a dosing interval
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
DERC	Dose-Escalation Review Committee
DFI	Dermatitis Family Index
DPT	Diphtheria, tetanus, pertussis
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI-50	≥50% improvement from baseline in EASI score
EASI-75	≥75% improvement from baseline in EASI score
EC	Ethics Committee
ECG	Electrocardiogram

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

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

SOC	System organ class
TARC	Thymus and activation regulated chemokine
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
US	United States
V	Volume of distribution
WBC	White blood cell
WOCF	Worst observation carried forward

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1. INTRODUCTION AND RATIONALE

1.1. 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 prevalence of AD in the first 2 years of life has been reported to be 21.5% (Ileli 2004). Phase 3 of the International Study of Asthma and Allergies in Childhood showed a 1-year period prevalence rate higher than 15% in the 6 to 7-year-old age group in Australia, England, and Scandinavia (Asher 2006). 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 younger 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).

Infants and young children with severe AD have a reported risk rate of around 60% for developing asthma later on in life compared to a risk of around 30% in patients with mild AD (Ricci 2006).

Atopic dermatitis is caused by a complex interaction of genetics, defects in skin barrier function, environmental exposure, and immunologic responses. Type 2 helper T cell (Th2) mediated immune response is believed to play a central role in the pathogenesis of AD. The skin lesions of AD are characterized by increased expression of proinflammatory Th2 cytokines, such as interleukin (IL)-4 and IL-13, and by skin infiltration of Th2 cells. The elevated IgE responses and eosinophilia observed in the majority of patients with AD reflects an increased expression of the Th2 cytokines IL-4 and IL-13 (Leung 1999). Type 2 helper T cell-associated cytokines regulate important barrier related functions, such as epidermal cornification and production of antimicrobial proteins. These cytokines inhibit the production of major terminal differentiation proteins, such as loricrin, filaggrin, involucrin, and the antimicrobial proteins human beta defensin 2 and 3, which in turn, is associated with development of AD (Howell 2007, Guttman Yassky 2011a, Guttman Yassky 2011b).

The Th2 cytokines also act on keratinocytes and induce production of chemokines, including chemokine (C-C motif) ligand 17 (also known as thymus and activation regulated chemokine [TARC]), and chemokine (C-C motif) ligand 26 (also known as eotaxin-3), which are chemo-attractants for Th2 cells and eosinophils; thus, perpetuating the inflammatory response. Since activation of IL-4 and IL-13 signaling precedes the release of proinflammatory mediators, antagonism of these cytokines has the potential to reduce the Th2 response and provide therapeutic benefit.

A study was recently conducted with the aim of identifying differences and similarities between cutaneous lymphocyte antigen (CLA) +ve, polarized T-cell subsets in children versus adults with AD. In this study, peripheral blood from children less than 5 years old was compared with that of adults with well-characterized moderate-to-severe AD, using flow cytometry. The study concluded that Th2 activation within skin-homing T cells might drive AD in children. Moreover, the spreading to additional Th subsets, particularly Th22, is seen in adults but not in children (Czarnowicki 2015). Based on the results of this study, it is speculated that therapeutics that target Th2 cytokines, such as dupilumab, might be particularly valuable in the pediatric population with AD.

There is currently a high unmet medical need for an effective therapy for AD with an acceptable safety profile in infants and young children who suffer with moderate-to-severe AD. Nonpharmacological management of AD, which includes environmental control measures (eg, avoidance of antigen and skin irritants) and skin care measures (eg, maintaining the hydration of the skin through the use of emollients) play a supportive role, especially in children with moderate-to-severe disease. Pharmacological management of AD in children is mainly limited to topical therapy with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). However, long-term use of TCS in children is not recommended because of the risk of irreversible skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, growth retardation, hypothalamic pituitary axis effects, etc). Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are also used in AD as an alternative to or in combination with TCS. However, both tacrolimus and pimecrolimus are not indicated for use in children <2 years of age. Moreover, the use of TCI is frequently associated with skin irritation. Furthermore, a possible increased risk of malignancy (lymphoma and skin cancers) has been noted for TCIs.

Systemic agents are used off-label in children (cyclosporine, systemic steroids, methotrexate, azathioprine, and mycophenolate mofetil). A recent survey conducted in Europe, "European

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Treatment of Severe Atopic Eczema in Children Taskforce (TREAT)" found that approximately 70% of respondents initiated systemic therapy for children with severe AD (Proudfoot 2013). All of these systemic agents have significant side effects in children, including stunted growth, diabetes, hypertension, osteoporosis (corticosteroids), myelosuppression and hepatotoxicity (methotrexate), nephrotoxicity and hypertension (cyclosporine), and gastrointestinal disturbances and leucopenia (azathioprine). Moreover, a high proportion of patients in which disease is initially controlled by systemic agents suffer from relapse soon after therapy is discontinued (Schmitt 2009).

Type 2 inflammation (including Th2 responses) and the dysregulated activation of Th2 cells have been recognized as the key underlying disease drivers of AD and other associated atopic/allergic diseases. Targeting the key upstream type 2 cytokines, IL-4 and IL-13, has the potential for treating the pathology of AD as well as other associated atopic/allergic diseases. Since activation of IL-4 and IL-13 signaling precedes the release of proinflammatory mediators, antagonism of these cytokines has the potential to reduce the type 2 inflammatory responses seen in AD and other associated atopic/allergic diseases. In addition, type 2/Th2 cytokines are believed to induce altered epidermal responses, inhibit terminal differentiation proteins, and produce and/or amplify the skin barrier defect in AD; therefore, antagonism of IL-4 and IL-13 signaling has the potential to restore barrier function.

Dupilumab is a novel targeted immunoregulatory agent that selectively and simultaneously inhibits IL-4 and IL-13 signaling by blocking the obligate shared component of the IL-4/IL-13 receptor complex. It is intended to inhibit key disease drivers to achieve clinical benefit without the side effects commonly observed with existing non-selective systemic immunosuppressants. Dupilumab has been approved for marketing in the US, EU, and Japan for treatment of moderate-to-severe AD in adults and adolescents.

Dupilumab, given subcutaneously (SC), is currently in clinical trials for multiple indications, including treatment of moderate-to-severe AD in patients intolerant of, or whose disease is not adequately controlled with, topical treatments. As of 28 March 2019, dupilumab clinical data in AD are available from 22 completed and 6 ongoing (phase 1, 2, and 3) studies in adult healthy subjects and in patients with AD. A total of 202 healthy subjects, and 3931 patients with AD have been exposed to dupilumab in phase 1, single-dose studies at doses up to 12 mg/kg intravenous (IV) and 600 mg SC, and phase 1 through 3 multiple-dose studies at doses up to 300 mg once a week (QW), preceded by a 600 mg loading dose. Sixteen of the 22 completed studies were conducted in patients with AD. Data from these studies showed rapid and dose-dependent improvement in pharmacodynamic (PD) and efficacy endpoints in dupilumab-treated patients. Dupilumab has also been consistently well-tolerated across these clinical studies.

Dupilumab has been studied in 2 completed studies in pediatric patients with AD. R668-AD-1412 was a phase 2 study investigating the safety, pharmacokinetics (PK), immunogenicity, and exploratory efficacy of dupilumab in patients aged ≥6 to <12 years with severe AD and ≥12 to <18 years with moderate-to-severe AD (77 patients were exposed to dupilumab). R668-AD-1526 was a phase 3 study investigating the efficacy and safety of dupilumab in patients ≥12 to <18 years of age with moderate-to-severe AD (166 patients were exposed to dupilumab). Data from these completed studies in pediatric patients with AD showed that dupilumab had an acceptable safety profile and was well tolerated in patients aged ≥6 to <18 years of age (see Section 1.2.3.2), and provided significant clinical benefit (Section 1.2.3.1).

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In addition, dupilumab is currently being studied in 2 other ongoing pediatric studies: a phase 3 study (R668-AD-1652) investigating the efficacy and safety of dupilumab administered concomitantly with TCS in patients 6 years to <12 years of age with AD, and an open-label extension (OLE) study (R668-AD-1434) to assess the long-term safety and efficacy of dupilumab in patients aged ≥6 months to <18 years with AD. Study R668 AD 1652 has completed the primary analysis period and the OLE study R668-AD-1434 has completed the secondary analysis period.

Dupilumab has also been studied in 2 completed (EFC13579 and EFC13691) and 1 ongoing (EFC14153) phase 3 double-blind, placebo-controlled studies evaluating the efficacy and safety of dupilumab in patients, including pediatric patients, with uncontrolled asthma (see Section 1.2.3.2).

In addition, pediatric patients aged ≥12 to <18 years (n=50) were included in study R668-AD-1607 (a phase 1b actual use study of dupilumab auto-injector device in patients with AD).

Completed and ongoing clinical studies with dupilumab in AD are further described in Section 1.2.3.

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

1.2. Rationale

1.2.1. 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 to support registration and labeling for the use of dupilumab in pediatric patients, 6 months to less than 6 years of age, suffering from moderate-to-severe AD, whose disease cannot be adequately controlled with topical medications, or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects, or safety risks).

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 moderate-to-severe AD. Part A is an open-label, single-ascending-dose, sequential cohort phase 2 study in patients ≥6 months to <6 years of age with severe AD. The primary objective of part A is to obtain safety and PK data in this patient population, to guide dose selection for part B.

In part A, all patients will receive treatment with dupilumab. This approach will minimize the number of patients required in the study to obtain adequate dupilumab PK and safety data.

The ascending dose cohort and descending age subset design in part A was chosen to allow the lower dose and older, less vulnerable age subset to be evaluated first. Review, at internal safety review meetings, of safety data from cohorts who have already been dosed before opening up a new cohort, will further ensure patient safety.

Part B is a randomized, double-blind, parallel-group, placebo-controlled study in which study treatments will be administered concomitantly with topical therapy to patients. The primary objective of part B is to demonstrate efficacy of dupilumab in combination with prescription topical therapy in pediatric patients, 6 months to less than 6 years of age, suffering from moderate-to-severe AD.

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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.

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.

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Given this background, a dose of 6 mg/kg in pediatric patients is expected to provide an exposure similar to a single dose of 300 mg in adult patients. This is supported by PK simulations using a PK model developed with data from adult AD patients and from pediatric AD patients in study R668-AD-1412 (A phase 2 study investigating the safety, PK, immunogenicity, and exploratory efficacy of dupilumab in patients aged ≥6 to <18 years with AD).

As part of the ascending-dose sequential cohort design, the dose regimen of 3 mg/kg was chosen as the initial starting dose to first evaluate the safety of dupilumab at the lower dose before progressing to the higher, 6 mg/kg, dose cohort. The first study with dupilumab in pediatric patients 6 to 17 years of age (R668-AD-1412) evaluated doses of 2 mg/kg and 4 mg/kg. A review of the data from this study showed that these doses were well tolerated with an acceptable safety profile, in addition to showing some clinical benefit. A dose of 3 mg/kg in patients 6 months to <6 years of age is expected to provide exposure lower than that seen with a dose of 4 mg/kg in patients 12 to 17 years of age in study R668-AD-1412.

In study R668-AD-1412, a trend for a higher incidence of persistent anti-drug antibodies (ADAs) was seen in the lower dose cohorts (2 mg/kg) compared to the higher dose cohorts (4 mg/kg). A lower dose is typically more immunogenic than a larger dose (European Medicines Agency 2007, Food and Drug Administration 2014) and the use of high-dose monoclonal antibodies (mAbs) has been shown to reduce immunogenicity and induce tolerance through exhaustion of the immune response (Maini 1998). Given this background, a starting dose of 3 mg/kg is expected to lower the likelihood of an immune response compared to a 2 mg/kg dose.

In part A of the current study (R668-AD-1539), 20 patients in the age group ≥2 to <6 years and 20 patients in the age group ≥6 months to <2 years were enrolled. Single-dose treatment with dupilumab 3 mg/kg or 6 mg/kg led to reduction in both signs (as measured by percent reduction in EASI score from baseline, proportion of patients achieving ≥50% improvement from baseline in EASI score [EASI-50]) and symptoms (as measured by percent reduction in pruritus numeric rating scale [NRS] from baseline) of AD. Mean body weight was 17.1 kg in the ≥2 to <6 years of age and 9.8 kg in the ≥6 months-<2 years age group.

- In the ≥2 to <6 years of age group, single doses of 3 mg/kg SC dupilumab provided a mean reduction from baseline in EASI score of 44.6% at week 3 and 26.6% at week 4 and single doses of 6 mg/kg SC dupilumab provided a mean reduction of 49.7% at week 3 and 48.7% at week 4.
- In the ≥6 months to <2 years of age group, single doses of 3 mg/kg SC dupilumab provided a mean reduction from baseline in EASI score of 42.7% at week 3 and 22.4% at week 4 and single doses of 6 mg/kg SC dupilumab provided a mean reduction of 38.8% at week 3 and 43.2% at week 4.

Single-dose treatment with dupilumab 3 mg/kg or 6 mg/kg had an acceptable safety profile and was well tolerated in both age groups.

The dupilumab treatment group in part B of the current study is a weight-tiered fixed-dose regimen of 200 mg Q4W SC for children with a baseline body weight ≥5 to <15 kg and 300 mg Q4W SC for children with a baseline body weight ≥15 to <30 kg.

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The dose regimen of 300 mg Q4W was evaluated in pediatric patients ≥6 to <12 years of age with severe AD in the ongoing phase 3 study, R668-AD-1652, which included 61 patients in the ≥15 to <30 kg weight range. In the primary analysis completed at the end of the treatment period, the 300 mg Q4W dose regimen led to clinically relevant and statistically significant reduction in both signs and symptoms of AD. In the ≥15 kg to <30 kg weight range:

- Approximately 30% of patients achieved an IGA score of 0/1 (total n=61) in the 300 mg Q4W treatment group compared to 13% patients for the same weight category in the placebo group (total n=63). Similarly, 75% of patients achieved an EASI-75 in the 300 mg Q4W treatment group compared to 28% patients in the placebo group.
- Approximately 55% of patients achieved an NRS reduction ≥4 points in the 300 mg Q4W treatment group compared to 12% of patients in the placebo group.

The 300 mg Q4W regimen was shown to have an acceptable safety profile and was well tolerated in these patients, supporting use of the same doses in younger AD patients with similar body weights.

The doses selected for part B of the study were based on PK data gathered from part A (patients ≥2 years to <6 years of age or ≥6 months to <2 years of age) and integrated in a population PK model for pediatric patients with observations in patients ≥6 to <12 years of age or ≥12 to <18 years of age. Supporting PK simulations using this pediatric population PK model are summarized below. The goal of dose selection for part B was to achieve dupilumab exposure in pediatric patients at steady-state equivalent to exposure in adults where tolerability and efficacy have been demonstrated.

In adults, dupilumab regimens of 300 mg Q2W and QW were both shown to be well tolerated and efficacious in Phase 3 studies. Hence, various weight-tiered regimens were simulated using an established population PK model with the aim of selecting pediatric regimens that 1) achieved a distribution (5^{th}, median, and 95^{th} percentile) of $C_{trough,ss}$ (lowest concentration in a dosing interval at steady-state) that was similar to or greater than that of the standard 300 mg Q2W regimen in adults and 2) for which predicated maximum concentrations at steady-state ($C_{max,ss}$) did not exceed the $C_{max,ss}$ obtained with the 300 mg QW regimens in adults.

The predicted 5^{th} percentile of $C_{trough,ss}$ for 200 mg Q4W SC in children ≥5 to <15 kg and 300 mg Q4W SC in children ≥15 to <30 kg were similar to the 5^{th} percentile of $C_{trough,ss}$ for adult and adolescent Q2W concentrations. The predicted 95^{th} percentile of $C_{max,ss}$ of 200 mg Q4W SC in children ≥5 to <15 kg and 300 mg Q4W in children ≥15 to <30 kg did not exceed the adult 300 mg QW $C_{max,ss}$.

Safety considerations in this study will be informed with data obtained from the IDMC for the remaining subjects in part A.

1.2.3. Risk/Benefits of Participating in the Study

1.2.3.1. Benefits

The efficacy of dupilumab was evaluated in multiple randomized, double-blind, placebo-controlled studies in adults. In addition, the efficacy of dupilumab was evaluated in separate randomized, double-blind, placebo-controlled studies carried out in adolescents and in pediatric patients ≥6 to <12 years old. In each of these studies, dupilumab demonstrated clinically meaningful and statistically significant improvements compared to placebo in disease activity measures assessing objective AD signs (IGA, EASI, SCORing Atopic Dermatitis [SCORAD], body surface area [BSA] affected by AD), subjective symptoms (eg, Pruritus NRS, Patient Oriented Eczema Measure [POEM]), and quality of life (Dermatology Life Quality Index [DLQI] in adults, Childrens' Dermatology Life Quality Index [CDLQI] in adolescents and patients ≥6 to <12 years old). These results formed the basis for approval of dupilumab for moderate-to-severe AD in adults worldwide, and in adolescents in US and EU.

A first-step analysis was conducted on data (data cutoff of 21 Apr 2018) from adolescent patients (≥12 to <18 years old) enrolled in the OLE study, R668-AD-1434. The results of this first-step analysis support the long-term efficacy of dupilumab in adolescent patients with moderate-to-severe AD.

A second-step analysis was conducted on data (data cutoff of 22 Jul 2019) from pediatric patients ≥6 to <12 years of age enrolled in the OLE study, R668-AD-1434. The results of this second-step analysis support the long-term efficacy of dupilumab in patients ≥6 to <12 years of age with AD.

Based on data available to date for part A of the current study, single-dose treatment with dupilumab 3 mg/kg or 6 mg/kg provided clinical benefit for both signs and symptoms in patients ≥2 to <6 years, as well as patients ≥6 months to <2 years, of age with severe AD (see Section 1.2.2).

1.2.3.2. Risks

The most common adverse drug reactions identified in the dupilumab adult AD clinical program were injection site reactions common (≥10%). Other common adverse reactions (≥1% and <10%) included conjunctivitis, allergic conjunctivitis, eye pruritus, blepharitis, oral herpes, and eosinophilia. In the completed adolescent AD studies and in the ongoing study in patients ≥6 to <12 years old, the safety profile was consistent with that reported in adults and there were no new safety signals detected with dupilumab in the adolescent population. An acceptable safety profile has also been demonstrated in adolescent patients enrolled in the asthma study EFC13579 (n=107).

The results of the first-step analysis of adolescent OLE study R668-AD-1434 also showed that long-term treatment with dupilumab was well tolerated in adolescent patients, with a long-term safety profile similar to that of adolescent patients treated with dupilumab for shorter durations.

The results of the second-step analysis of the OLE study R668-AD-1434 also showed that long-term treatment with dupilumab was well tolerated in pediatric patients ≥6 to <12 years old, with a long-term safety profile similar to that of adolescent patients treated with dupilumab for a similar duration.

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In part A of the current study, single-dose treatment with dupilumab 3 mg/kg or 6 mg/kg appeared to be well tolerated in patients aged ≥2 to <6 years. The incidence of TEAEs was comparable in patients in the 3 mg/kg and 6 mg/kg dose groups (3/10 [30%] and 2/10 [20%], respectively). None of these events was severe. One patient had a serious TEAE of anaphylactic reaction. This event was assessed as not related to dupilumab, as an alternate cause for the event was present (history of allergy to nuts and patient had consumed nuts just prior to onset of event).

Moreover, in part A of the current study, single-dose treatment with dupilumab 3 mg/kg or 6 mg/kg also appeared to be well tolerated in patients aged ≥6 months to <2 years. The incidence of TEAEs was comparable in patients in the 3 mg/kg and 6 mg/kg dose arms (7/10 [70%] for each treatment regimen). The only TEAE that was reported in >2 patients was nasopharyngitis. One patient had a serious TEAE of anaphylactic reaction, which was assessed as not related to dupilumab as an alternate cause for the event was present (had consumed shell fish [crab] just prior to onset of event).

Overall, systemic hypersensitivity has been established as an important identified risk with dupilumab. As protein therapeutics, all monoclonal antibodies (mAbs) are potentially immunogenic. Rare serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD and anaphylaxis related to dupilumab in the adult asthma clinical studies. No event of serum sickness/serum sickness-like reaction or anaphylaxis related to dupilumab has been reported in the adolescent AD program.

In study R668-AD-1539, patients will be monitored at the study center for 2 hours post-dose for the first 3 visits at which study drug is administered to facilitate detection and treatment of any immediate hypersensitivity reactions to the study drug.

An important potential risk "Eosinophilia associated with clinical symptoms" has been observed in the asthma clinical trials (few cases of eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia) but not in AD clinical studies.

Nonclinical repeat-dose toxicity studies and reproductive and developmental toxicity studies have not identified any general or reproductive toxicology or postnatal effects of anti-IL-4 receptor subunit alpha (anti-IL-4Rα) surrogate antibodies in cynomolgus monkeys and mice. These nonclinical data, together with the clinical safety profile of dupilumab to date, support the evaluation of dupilumab in pediatric patients.

1.2.3.3. Risk/Benefit Conclusion

The safety data and the clinical benefit of dupilumab demonstrated in part A of this study as well as in multiple AD studies in adult, adolescent, and pediatric (≥6 to <12 years of age) patients, support a favorable benefit-risk profile for dupilumab.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective for part A of the study is to characterize the safety and PK of dupilumab administered as a single dose in pediatric patients, 6 months to less than 6 years of age, with severe AD.

The primary objective for part B of the study is to demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in pediatric patients, 6 months to less than 6 years of age, with moderate-to-severe AD.

2.2. Secondary Objectives

The secondary objective of part A of the study is:

- To evaluate the efficacy and immunogenicity of a single dose of dupilumab in patients 6 months to less than 6 years of age with severe AD

The secondary objective of part B of the study is:

- To assess the safety and immunogenicity of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in patients 6 months to less than 6 years of age with moderate-to-severe AD

2.3. Other Objectives

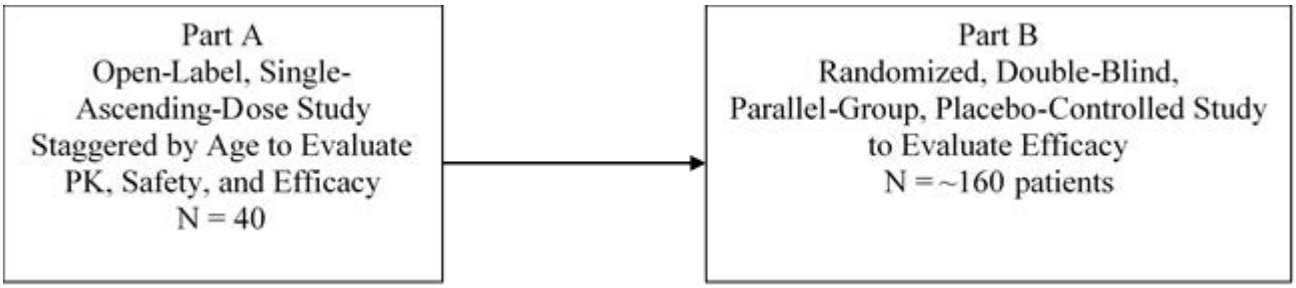
The other objectives of part B of the study is:

- To assess the concentrations of dupilumab in serum following repeated SC dosing.
- To assess the effects of dupilumab on blood and skin biomarkers of inflammation in comparison with placebo.
- To study dupilumab's mechanism of action (related to efficacy and/or safety), why some patients respond better than others (safety and/or efficacy), type 2 inflammation, as well as AD and related diseases.

3. STUDY DESIGN

3.1. Study Description and Duration

This study will be conducted in 2 parts:



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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).

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.

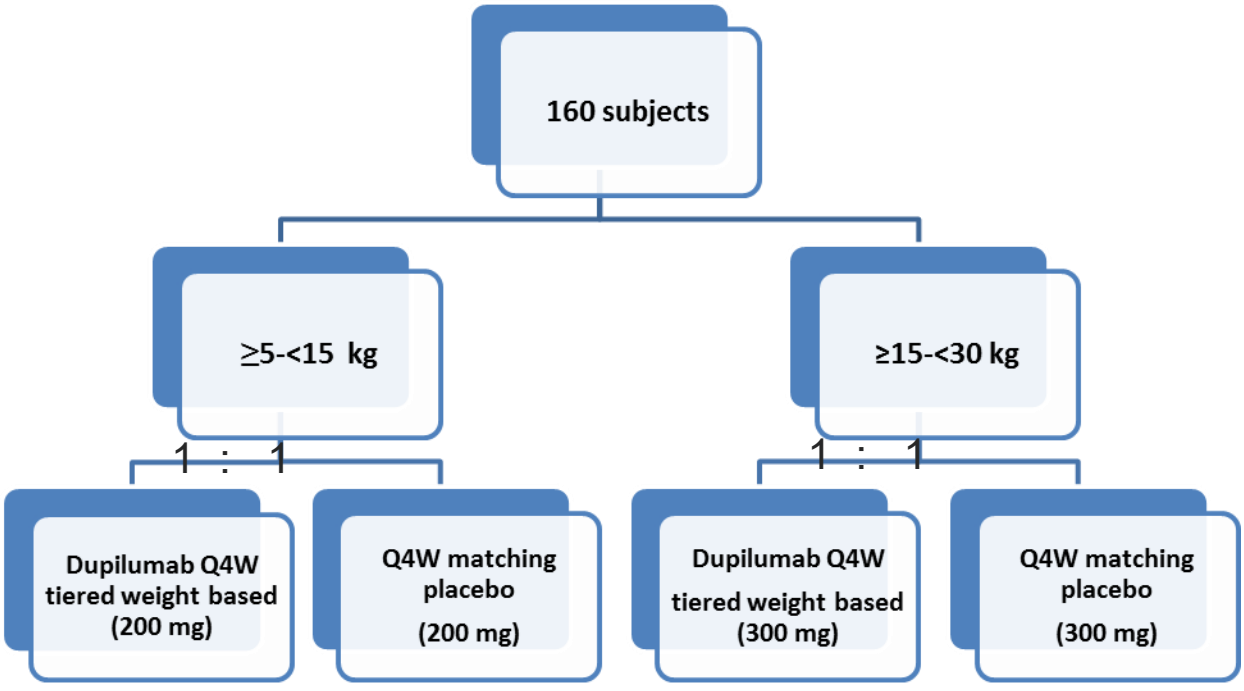
Patients will be required to apply moisturizers twice daily for at least 7 days before randomization (not including the day of randomization) and continue throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin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

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments. Patients 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 and 4), and region/country (North America, Europe, Japan, and China). The number of patients with moderate AD (IGA=3) will be capped at approximately 40. Approximately 160 patients will be randomized to 1 of the following 2 treatment regimens:

- dupilumab Q4W tiered fixed-dose (200 mg or 300 mg) treatment regimen:
  - Patients with baseline weight ≥5 to <15 kg will receive an SC injection of 200 mg dupilumab (1.14 mL of a 175 mg/mL solution) on day 1 and then 200 mg Q4W from week 4 to week 12.
  - Patients with baseline weight ≥15 to <30 kg will receive an SC injection of 300 mg dupilumab (2 mL of a 150 mg/mL solution) on day 1 and then 300 mg Q4W from week 4 to week 12.
- placebo Q4W treatment regimen: patients will receive matching placebo on day 1 and then Q4W from week 4 to week 12.
  - In the ≥5 to <15 kg weight stratum, patients randomized to placebo will receive Q4W injections of placebo (1.14 mL) matching 200 mg dupilumab.
  - In the ≥15 to <30 kg weight stratum, patients randomized to the placebo group will receive Q4W SC injections of placebo (2 mL) matching 300 mg dupilumab.

Figure 1 shows the randomization scheme for part B of the study.

Figure 1: Randomization Scheme (Part B)



Note: 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).

Starting on day -14, all patients will be required to initiate treatment with low potency TCS using a standardized regimen (see Section 5.2 for details).

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

Safety and laboratory assessments, samples for dupilumab concentration and ADA response to dupilumab, and efficacy assessments will be performed or collected at specified time points throughout part B of the study according to the schedule described in Table 2. The end of treatment period visit will occur at week 16, 4 weeks after the last dose of study drug. The co-primary endpoints (proportion of patients with an EASI-75 is a co-primary endpoint for EU and EU Reference Market Countries only, key secondary endpoint for US) will be assessed at this visit. The study procedures and assessments for patients enrolled in Japan and China will be the same as for other patients enrolled outside of Japan and China.

An OLE study (R668-AD-1434) in patients aged 6 months to <18 years old is currently ongoing. Patients who complete the treatment period in part B may subsequently be eligible to participate in the OLE study (see Section 5.8 for details).

Patients who decline to participate in the OLE will enter a follow-up period of 12 weeks. Follow-up visits will occur every 4 weeks from week 20 through week 28. During the follow-up period, patients will be monitored for safety and tolerability and have laboratory and clinical assessments as listed in the schedule of events, Table 2. 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 may be asked to return to the clinic to have additional blood samples collected for ADA analysis.

Patients will also undergo sparse blood sample collection for characterizing the repeat dose serum trough concentrations of dupilumab during part B.

Tape stripping samples may be taken for exploratory biomarker analysis from patients whose parent(s) or legal guardian(s) consent for the child to participate in this optional sub-study at a subset of study sites (see Section 6.2.7.2). Patient participation in a tape stripping sub-study in part B 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 ICF (see Section 6.2.7.3). Patient participation in the genomics sub-study in part B is optional.

Patient participation in the vaccination sub-study in part B is optional. Patients' parents or legal guardians who plan to have their children vaccinated during the study and agree to enroll them in the optional sub-study, will sign a separate vaccination sub-study ICF for the collection of 2 blood samples for assay of vaccine immunoglobulin G (IgG) in serum for each vaccine administered (see Section 6.2.1).

Figure 2: Study Flow Diagram (Part A)

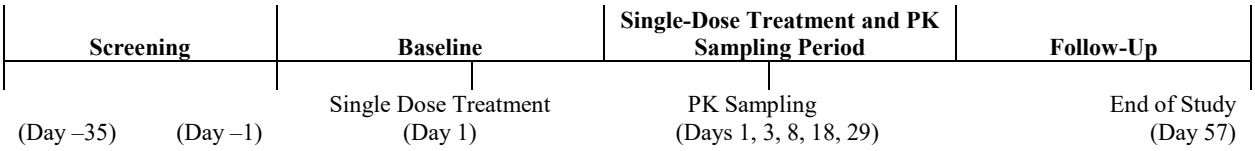
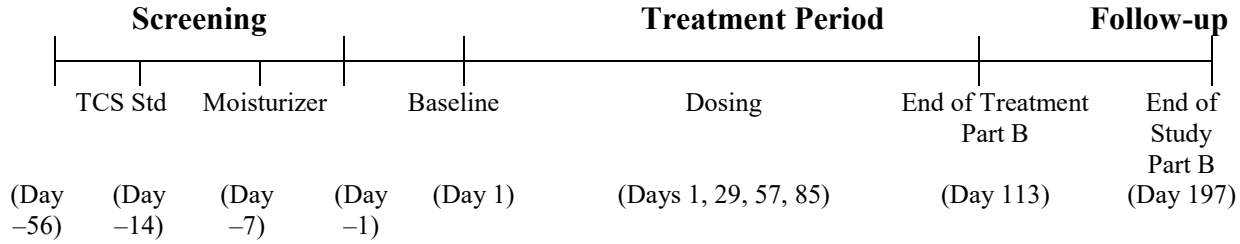


Figure 3: Study Flow Diagram (Part B)



TCS Std: topical corticosteroid standardization

Note: The length of the screening period is not fixed but must not exceed 56 days (including TCS standardization). The length of the TCS standardization period is fixed at 14 days. Moisturizers are to be applied at least twice daily during the 7 consecutive days prior to randomization (not including day of randomization) and are to be used throughout the study. At least 11 of the 14 total applications of moisturizers prior to randomization must be applied for the patient to remain eligible for the study.

3.1.1. Study Cohorts

Study cohorts will only be used in part A of the study.

In part A, 2 sequential ascending age cohorts are planned: age cohort 1 (≥6 months to <2 years) and age cohort 2 (≥2 to <6 years). Each age cohort will consist of approximately 20 patients (an approximate total of 10 patients in 2 dose sub-cohorts): sub-cohort A (dose of 3 mg/kg) and sub-cohort B (dose of 6 mg/kg):

- Cohort 1A: children age cohort (≥2 to <6 years), dose sub-cohort 3 mg/kg SC
- Cohort 1B: children age cohort (≥2 to <6 years), dose sub-cohort 6 mg/kg SC
- Cohort 2A: children age cohort (≥6 months to <2 years), dose-sub-cohort 3 mg/kg SC
- Cohort 2B: children age cohort (≥6 months to <2 years), dose sub-cohort 6 mg/kg SC

3.1.2. Dose Escalation and Study Stopping Rules

Dose escalation and stopping rules are only applicable to part A of the study.

A Dose-Escalation Review Committee (DERC) will be established for the purpose of dose escalation during part A of the study (see Section 3.3.2 for details on committee membership).

The DERC will meet at the following pre-defined time points:

1. When all of the patients enrolled in cohort 1A have completed the week 4 (day 29) safety assessments
2. When all of the patients enrolled in cohort 2A have completed the week 4 (day 29) safety assessments

During these meetings, the DERC will review all available safety data from completed cohorts. This will include data on AEs (including SAEs and adverse events of special interest [AESIs]), vital signs, and laboratory values. The DERC will monitor AEs including, but not limited to, serious infections, severe injection site reactions, systemic immune reactions like hypersensitivity and severe conjunctivitis.

Dose escalation to the next cohort will not immediately proceed if the following occurs:

- If 2 or more patients in a cohort experience a severe AE that is deemed related to study drug by the investigator

If this occurs, the DERC will evaluate all of the available safety information and inform senior scientific leadership at Regeneron who will make the final recommendation on dose escalation to the next cohort.

For other unanticipated safety findings, the DERC, at their discretion, may defer to the senior scientific leadership at Regeneron for the decision on dose-escalation to the next cohort.

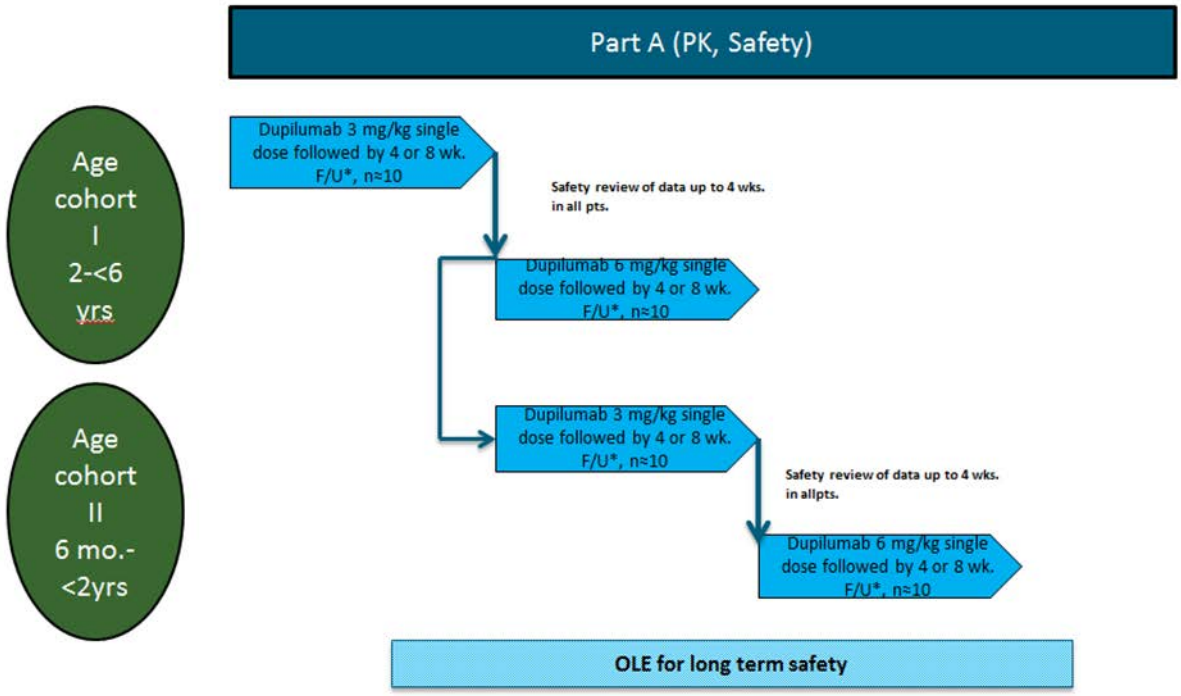
In addition to the pre-defined time points mentioned above, DERC will also meet on an ad-hoc basis if the following occurs:

- A treatment-emergent SAE occurs that is assessed by the investigator or the sponsor to be related to dupilumab treatment

In this instance, a comprehensive review of the data gathered from the patient(s) in whom the SAE(s) occurred will be performed. In addition, review of all safety data gathered from the study available at the time of the meeting will be performed. Based on this review, DERC will inform senior scientific leadership at Regeneron who will make the final recommendation on whether to continue the study as planned, or to terminate the study.

The dose escalation scheme in part A is presented in Figure 4.

Figure 4: Study Design and Dose Escalation Scheme (Part A)



Note: cohort 1A: ≥2 to <6 years of age, 3 mg/kg dose; cohort 1B: ≥2 to <6 years of age, 6 mg/kg dose; cohort 2A: ≥6 months to <2 years of age, 3 mg/kg dose, cohort 2B: ≥6 months to <2 years of age, 6 mg/kg dose

Patients will be offered an opportunity to participate in an OLE study at week 4. Patients who decline the OLE study will be followed up for an additional 4 weeks.

3.1.3. End of Study Definition

The end of study is defined as the last visit for the last patient in part B.

3.2. Planned Interim Analysis

No interim analysis with alpha spending is planned.

However, an unblinded primary analysis (see Section 9.5.2.4) **may** be performed once all patients in part B 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 primary analysis will be considered the final analysis for the primary and secondary efficacy endpoints. The submission of marketing applications to some regulatory authorities will be supported by these week 16 data.

A description of the statistical methods to be employed and blinding implications are in Section 9.5.2.4.

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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

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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.

* TCIs are not permitted during the 2-week TCS standardization period. Investigators may substitute TCIs with low potency steroids on areas of skin on which TCIs are typically applied (eg, face, neck, intertriginous, and genital areas).

NOTE: The target population with respect to disease severity differs for part A (severe AD) and part B (moderate-to-severe AD). Therefore, disease severity criteria are specified separately for part A and part B in inclusion criterion 4 to 6 below:

4. IGA score at screening and baseline visits:
   a. part A: IGA = 4
   b. part B: IGA ≥3
5. EASI score at screening and baseline visits
   a. part A: EASI ≥21
   b. part B: EASI ≥16
6. BSA involvement at screening and baseline visits:
   a. part A: ≥15%
   b. part B: ≥10%
7. At least 11 (of a total of 14*) applications of a topical emollient (moisturizer) during the 7 consecutive days immediately before the baseline visit (not including the day of randomization) (**for part B of the study only**)

   * Based on application of moisturizer twice daily for 7 days leading up to randomization. Application of emollient more than twice in a day is permitted but the additional applications will not be counted in the 11 required applications to fulfil eligibility for the study.
8. Parent(s) or legal guardian (s)-provided signed informed consent. Assent collected from patient, if applicable, as per local regulatory (competent authority/ethics) guidelines, based upon the age and level of maturity of the patient.
9. Parents/caregiver or legal guardians, as appropriate, are able to understand and complete the study requirements and study-related questionnaires
10. Baseline worst scratch/itch score weekly average score for maximum scratch/itch intensity ≥4 (**for part B of the study only**)

    NOTE: Baseline worst scratch/itch average score for maximum itch intensity will be determined based on the average of daily worst scratch/itch NRS scores for maximum scratch/itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization (does not include the day of randomization). A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. A daily score consists of answers to the following question.

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

    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 56-day maximum duration for screening.

11. At least 11 (of a total of 14) daily applications of low potency TCS during the 2-week TCS standardization period (beginning on day -14) leading up to the baseline visit (**for part B of the study only**).

4.2.2. Exclusion Criteria

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

1. Prior treatment with dupilumab.
2. History of important side effects of low potency topical corticosteroids (eg, intolerance to treatment, hypersensitivity reactions to hydrocortisone 1%/hydrocortisone acetate 1% cream*, significant skin atrophy, systemic effects), as assessed by the investigator or patient's treating physician (**only applicable for part B of the study**).

   *If a patient has a history of hypersensitivity reaction to hydrocortisone acetate 1% cream, and/or other ingredient in the particular TCS drug product, the patient can still be randomized if the investigator believes the patient can be safely treated during the study with a different low potency TCS drug product that does not have cross-reactivity to the drug product that caused the hypersensitivity (see Section 5.2 for further details).
3. Treatment with a topical investigational drug within 2 weeks or within 5 half-lives (if known), whichever is longer, or treatment with a systemic investigational drug prior to the baseline visit.

   NOTE: Treatment with a systemic investigational drug refers to treatment received in a clinical study with a drug that is not yet available on the market.
4. Treatment with a TCI within 2 weeks prior to the baseline visit (**only applicable for part B of the study**)
5. Having used any of the following treatments within 4 weeks, or within a period equal to 5 times the half-life of the drug, before the baseline visit, whichever is longer:
   a. Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
   b. Phototherapy for AD
6. Treatment with biologics, as follows:
   a. Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte and CD 19+ lymphocyte count returns to normal, whichever is longer
   b. Other biologics: within 5 half-lives (if known) or 16 weeks, whichever is longer
7. Treatment with crisaborole within 2 weeks prior to the baseline visit **(only applicable for part B of the study)**

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8. Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit

   NOTE: For patients who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a pediatrician, whether the administration of a live (attenuated) vaccine can be postponed until after the end of study, or preponed to before the start of the study, without compromising the health of the patient:

   a. Patients for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.

   b. Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

   Note: This exclusion criterion is not applicable to inactivated vaccines (eg, diphtheria, tetanus, pertussis [DPT], hepatitis A, hepatitis B, inactivated polio vaccine [IPV], hemophilus influenza type b, meningococcal, pneumococcal, and flu shot) which are permitted during the study as well as during the screening period, without any requirement of washout prior to baseline visit.

9. Planned or anticipated use of any prohibited medications and procedures during study treatment.

10. Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit) (**for part B of the study only**).

11. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the baseline visit.

    NOTE: Patients may be rescreened after infection resolves. A patient with mild, localized superficial infection can be included in the study based on investigator discretion.

12. Established diagnosis of a primary immunodeficiency disorder (eg, Severe Combined Immunodeficiency, Wiskott Aldrich Syndrome, DiGeorge Syndrome, X-linked Agammaglobulinemia, Common Variable Immunodeficiency), or secondary immunodeficiency. Patients suspected to have immunodeficiency based on their clinical presentation (history of invasive opportunistic infections eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, chronic mucocutaneous candidiasis etc. or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the investigator) will also be excluded from the study.

13. Eczema as part of a genodermatosis syndrome like Netherton's syndrome, Hyper IgE syndrome, Wiskott Alrdich syndrome etc.

14. Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit.

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15. Established diagnosis of Hepatitis B viral infection at the time of screening or who are positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb), at time of screening.

    NOTE: Patients who are HBsAg negative and hepatitis B surface antibody (HBsAb) positive are considered immune after a natural infection has cleared or they have been vaccinated against hepatitis B. Therefore, they are acceptable for the study. These patients will be allowed to enroll into the study but will be followed using routine clinical and liver function tests.

16. Established diagnosis of hepatitis C viral infection at the time of screening or who are positive for hepatitis C antibody at the screening visit.

17. History of past or current tuberculosis or other mycobacterial infection.

    Note: Irrespective of status of treatment or infection resolution. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethic committees.

18. Have known hepatic disease or are on current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure, or has evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥2 weeks apart), elevated transaminases (alanine aminotransferase [ALT], and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal [ULN] during the screening period.

19. Presence of any one or more of the following abnormalities in laboratory test results at screening:

    - Platelets $\leq 100 \times 10^3/\mu L$
    - Neutrophils $\leq 1.0 \times 10^3/\mu L$ for patients <1 year of age; Neutrophils $\leq 1.5 \times 10^3/\mu L$ for patients 1 year to <6 years of age
    - Eosinophils >5000/µL
    - Creatine phosphokinase (CPK) >2.5×ULN
    - Serum creatinine >1.5×ULN

    NOTE: If an abnormal value is detected at screening, a repeat test should be performed to confirm the abnormality. If the repeat test confirms the abnormality, the patient will be categorized as a screen failure.

20. Presence of skin comorbidities that may interfere with study assessments. This includes, but is not limited to, conditions like scabies, seborrheic dermatitis, cutaneous T cell lymphoma, psoriasis, etc.

21. History of malignancy at any time before the baseline visit.

22. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.

23. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to patients with short life expectancy, patients with major congenital malformations, patients with cardiovascular conditions (eg, major, clinically significant congenital cardiovascular abnormalities), severe renal conditions, hepato-biliary conditions (eg, Child-Pugh class B or C), active major autoimmune diseases (eg, lupus, inflammatory bowel disease etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary, neurological or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRF], etc).
24. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRF, etc).
25. Planned major surgical procedure during the patient's participation in this study.
26. Member of the investigational team or his/her immediate family.
27. Body weight <5 kg or ≥30 kg at baseline (**only applicable part B of the study**).

4.3. Premature Withdrawal from the Study

A patient/parent or legal guardian has the right to withdraw the patient from the study at any time, for any reason, and without repercussion.

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

Patients who withdraw prematurely from the study will be asked to complete study assessments per Section 6.1.1.

4.4. Replacement of Patients

In part A, patients who are prematurely withdrawn from the study prior to completing the single dose PK sample collection (ie, prior to week 4, part A) may be replaced, if needed, to ensure an adequate number of evaluable patients. The medical monitor, in cooperation with the study statistician and PK scientist, will decide if a patient who prematurely withdraws from the study should be replaced.

Patients prematurely discontinued from the study in part B will not be replaced.

5. STUDY TREATMENTS

Study drug treatment will be administered by study site personnel. Background and rescue treatments will be applied by the patient's caregiver.

5.1. Investigational and Reference Treatments

Part A

Sterile dupilumab (REGN668) drug product 150 mg/mL will be provided in an aqueous buffered vehicle, pH 5.0. It will be supplied in a 5-mL vial containing 2.5 mL (150 mg/mL) with a withdrawable volume of 2.0 mL or 300 mg of dupilumab. Instructions on dose preparation are provided in the pharmacy manual.

Study drug will be administered SC by the investigator or other qualified study personnel at the following dose and dosing schedules for part A:

- For dose cohort 1A: 3 mg/kg at day 1 as a single dose
- For dose cohort 1B: 6 mg/kg at day 1 as a single dose
- For dose cohort 2A: 3 mg/kg at day 1 as a single dose
- For dose cohort 2B: 6 mg/kg at day 1 as a single dose

Part B

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

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

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

- 1.14 mL placebo matching 200 mg dupilumab formulation
- 2 mL placebo matching 300 mg dupilumab formulation

Patients will be randomized to receive either dupilumab (tiered fixed dose by body weight stratum: 200 mg [patients ≥5 to <15 kg] or 300 mg [patients ≥15 to <30 kg]) Q4W or placebo Q4W. Refer to Section 3.1 for further details.

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

Patients will be monitored at the study site for a minimum of 2 hours after the first 3 doses of study drug (visits 3 [day 1/baseline], 7 [week 4]), and 11 [week 8]; vital signs (sitting systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) and AE assessments will be done at 30 minutes (±10 minutes) post dose and then at 2 hours (±15 minutes).

Instructions on dose preparation are provided in the pharmacy manual.

5.2. Background Treatments

Background treatment will only be required to be used by patients in part B of the study.

In part B of the study, all patients are required to have moisturizers (emollients) applied at least twice daily for at least the 7 consecutive days immediately before randomization (does not include day of randomization). At least 11 of the 14 total applications must be applied for the patient to remain eligible for the study. Patients are to continue to have moisturizers applied throughout the remainder of the study (all 28 weeks where applicable). However, to allow adequate assessment of skin dryness, moisturizers should not be applied for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives 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 in part B are required to initiate treatment with TCS using a standardized regimen according to the following guidelines:

- Apply low potency TCS once daily to areas with active lesions. Based on investigator discretion, low/mild potency TCS may also be used on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.).
- Once the patient achieves an IGA score of 2 or less, lower frequency of use of low potency TCS to 3 times per week, and then stop once lesions are clear (IGA=0). Patients should be instructed to only use TCS on active lesions, and to stop use of TCS if lesions clear completely in between clinic visits.
- If lesions return, reinstitute treatment with low potency TCS, with the same step-down approach described above upon lesion resolution.
- For lesions persisting or worsening under daily treatment with low potency TCS, patients may be treated (rescued) with medium or high potency TCS (super potent TCS are not allowed to be used, even as rescue, see Section 5.3). The use of medium or high potency TCS as rescue is only allowed after day 14. A medium or high potency TCS should normally be restricted to use on non-delicate skin sites (excluding face, flexures, groin), and should not be used for a prolonged period in order to prevent the development of cutaneous atrophy and adrenal axis suppression. Low potency steroids should normally be used for delicate skin sites (face, flexures, groin) during these flares. Topical calcineurin inhibitors may be used for rescue, alone or in combination with TCS, but the use of TCIs should be reserved for problem areas only (eg, face, neck, intertriginous, and genital areas, etc).

Steroids that can be used during the study are described below and in Appendix 2. The use of TCS should be consistent with the product label. The use of very high potency or super potent TCS is prohibited during the study, as their use is not recommended in patients under 12 years of age. If patients have tolerance issues with any of these steroids, and/or to the excipients in a particular formulation (eg, hypersensitivity), or if they are not commercially available in some countries, they may substitute with products of the same potency from the list provided in the investigator site binder. It is required that patients use hydrocortisone acetate 1% cream for low potency (hydrocortisone 1% cream can be used in case the acetate salt is not available). Only in case of known side effects to hydrocortisone 1%/ hydrocortisone acetate 1% cream (eg, for hypersensitivity) or in case of non-availability due to any reason, other low potency TCS such as alclometasone dipropionate 0.05% cream or desonide 0.05% cream can be used.

If rescue with TCS is needed, it is recommended that patients use triamcinolone acetonide 0.1% ointment for medium potency. Other medium to high potency TCS can be used as per investigator discretion. (Please refer to Appendix 2 for a list of such agents).

- It is required that moisturizers be applied twice daily during the 7 consecutive days immediately before randomization (does not include day of randomization) and patients are to continue to apply moisturizers throughout the study (once in the morning and once in the evening). A 60-minute interval between the application of emollients and TCS is recommended wherever applicable.
- Patients will return TCS tubes at each clinic visit through week 16, and these tubes will be weighed by the site staff to determine the actual amount of TCS used.

5.3. Rescue Treatments

Rescue treatment for worsening of AD may be provided to study patients at the discretion of the investigator in parts A and B of the study. The use of rescue treatment is only allowed after day 14 of the study **in part B**. Investigators will be required to perform an IGA assessment prior to starting rescue treatment and initiate rescue treatment only in patients who either have an IGA score ≥3 or have intolerable symptoms. If possible, investigators are encouraged to consider rescue initially with topical treatment (eg, medium or high potency TCS) and to escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. Topical calcineurin inhibitors may be used for rescue, alone or in combination with TCS, but the use of TCIs should be reserved for problem areas only (eg, face, neck, intertriginous, and genital areas, etc). Investigators may also consider rescue with crisaborole. Rescue treatment for these topical therapies should be used as per prescribing information and local guidelines. Patients may continue study treatment if rescue consists of topical medications.

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

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pre-specified algorithm will be used to classify rescue (details in the Statistical Analysis Plan). In addition, a blinded review of all post-baseline medications to adjudicate rescue treatment, based on medical judgement, will be performed to adjudicate rescue. Patients who receive rescue treatment as per this adjudication during the study will be considered treatment failures.

5.4. Dose Modification and Study Drug Discontinuation Rules

5.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

5.4.2. Study Drug Discontinuation

The study drug discontinuation criteria are only applicable to part B of the study as patients receive a single dose of study drug in part A. Patients who permanently discontinue from study drug and who do not withdraw from the study in part B, will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who opt to withdraw from the study (see Section 4.3) will be asked to complete study assessments, per Section 6.1.1.

5.4.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Anaphylactic reaction or other severe systemic reaction to the study drug
- Diagnosis of a malignancy during study
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5\times10^3$ µL
  - Platelet count $\leq 50\times10^3$ µL
  - ALT and/or AST values greater than 3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5×ULN (for more than 2 weeks)

  NOTE: If the laboratory abnormality is considered causally related to study drug, study treatment will be permanently discontinued. In cases in which a causal relationship to study drug can be reasonably excluded, (ie, an alternative cause is evident), study treatment will be discontinued but it may be resumed when the laboratory abnormality is sufficiently normalized. A decision to resume study treatment will be made jointly by the investigator and medical monitor (medical monitor's written approval is required).

- Treatment with any prohibited concomitant medication or procedure (Section 5.7.1)

  NOTE: The use of TCI and crisaborole is prohibited during the 2 weeks of TCS standardization during part B (beginning on day -14 of the screening period) leading up the baseline visit, and during the treatment period. The use of very high potency or super potent TCS is not allowed throughout the study (as their use is not recommended in patients under 12 years of age). However, medium or high-potency TCS, TCIs, and crisaborole can be used as rescue treatment (see Section 5.3). In this situation, the study drug may be continued. Patients who receive systemic corticosteroids or systemic non-steroid immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc) as rescue medication during part B of the study, will be discontinued permanently from the study drug.

5.4.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - ALT or AST >3×ULN and ≤5xULN
  - Neutrophils $\leq 1.0\times10^3/\mu L$, but $>0.5\times10^3/\mu L$ for patients <1 year of age; Neutrophils $\leq 1.5\times10^3/\mu L$, but $>0.5\times10^3/\mu L$ for patients 1 year to <6 years of age
  - Platelet count $\leq 100\times 10^3/\mu L$ but $>50\times10^3/\mu L$
  - Eosinophils >5000/µL
  - CPK >2.5×ULN
  - Serum creatinine >1.5× ULN
- Other intercurrent illnesses or major surgery
- An infection that requires parenteral treatment or oral treatment for longer than 2 weeks with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents

After the condition leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. A decision to discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. The investigator may suspend study treatment at any time, even without consultation with the medical monitor, if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

5.5. Method of Treatment Assignment

Part A of the study is open-label; all patients will receive dupilumab. 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 B of the study is a randomized, double-blind, parallel group, placebo-controlled study in which approximately 160 patients will be randomized in a 1:1 ratio stratified by baseline weight (≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3, 4), and region/country (North America, Europe, Japan, and China) to receive 1 of the following 2 treatment regimens.

- dupilumab Q4W tiered fixed-dose (200 mg for patients ≥5-<15 kg or 300 mg for patients ≥15-<30 kg) regimen
- placebo Q4W regimen

Randomization will be performed according to a central randomization scheme provided by an IWRS to the designated study pharmacist (or qualified designee). Randomization slots will be reserved for patients from Japan and China in the IWRS. The number of patients with moderate AD (IGA=3) will be capped at approximately 40.

5.5.1. Blinding

Part A of the study is open-label, therefore blinding procedures will not be implemented.

Part B of the study, except for IDMC members and the provisions specified in Section 5.5.2, will remain blinded to all individuals until the prespecified unmasking to conduct the primary analyses.

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

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

5.5.2. Emergency Unblinding

In part B of the study, unblinding of treatment assignment for a patient may be necessary due to a medical emergency, an SAE that is unexpected and for which a causal relationship to the study drug cannot be ruled out, or for any other significant medical event.

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

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

In part A of the study, open-label study drug will display the product lot number on the label.

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

Study drug will be stored at the site at a temperature of 2º to 8ºC; storage instructions will be provided in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2º to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee.

5.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

5.6.4. Treatment Compliance

In part B of the study, all drug compliance records, including information collected by parents/caregivers in the dosing electronic diary (e-diary), must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.7. Concomitant Medications and Procedures

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

5.7.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited during the study. Study drug will be immediately discontinued if any of the following are used during the study:

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

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

  NOTE: Treatment with an inactivated vaccine (eg, DPT, hepatitis A, hepatitis B, IPV, hemophilus influenza type b, meningococcal, pneumococcal, and flu shot) is permitted during the study as well as during the screening period, without any requirement of washout prior to baseline visit.

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating biologics
- Treatment with systemic nonsteroidal immunosuppressant (may be used as rescue, see Section 5.3 for details)
- For part A:
  - Treatment with high potency or very high potency topical corticosteroids (high potency steroids may be used as rescue, see Section 5.3 for details). The investigator site binder will provide a list of steroids that fall under these classes.
- For part B:
  - Treatment with medium potency, high potency, or very high potency topical corticosteroids (medium or high potency steroids may be used as rescue, see Section 5.3 for details. A course of treatment with medium potency TCS may also be given during the screening period to demonstrate inadequate response to TCS and confirm eligibility for the study as per Section 4.2.1). The investigator site binder will provide a list of steroids that fall under these classes.
  - Treatment with TCI* (may be used as rescue, see Section 5.3 for details)

    *Use is not permitted during the 2-week screening period leading up to the baseline visit, the treatment, and follow-up periods

  - Treatment with crisaborole** (may be used as rescue, see Section 5.3 for details)
    **Use is not permitted during the 2-week screening period leading up to the baseline visit, the treatment, and follow-up periods
- Initiation of treatment of AD with prescription moisturizers

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy (ultraviolet A and/or ultraviolet B)

5.7.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 5.7.1, treatment with concomitant medications are permitted during parts A and B of the study. This includes basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment in part B), topical anesthetics, antihistamines, and topical and systemic anti-infective medications for any duration.

The use of TCS will be permitted as a standardized regimen for part B (see Section 5.2 for details). The use of TCS is also permitted during part A. It is recommended that patients use TCS of medium potency during part A (see investigator site binder for listing of TCS by class). The use of TCS should be consistent with local country guidelines and product prescribing information.

The use of TCIs is also permitted during part A, and during the screening period of part B, with the exception of the 2-week period leading up to the baseline visit. However, TCI should be reserved for problem areas (eg, face, intertriginous, and genital areas). The use of TCIs should be consistent with local country guidelines and product prescribing information. Topical corticosteroids and TCI should not be used concomitantly to treat the same affected areas.

The use of crisaborole is also permitted during part A, and during the screening period of part B, with the exception of the 2-week period leading up to the baseline visit. The use of crisaborole should be consistent with local country guidelines and product prescribing information.

Use of prescription moisturizers and moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products, is allowed as long as the use of such moisturizers has already been initiated before the screening visit. Initiation of treatment of AD with such moisturizers during the study is not allowed.

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

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

For Patients Enrolled in Part A

Patients who complete the PK sampling period of part A (ie, through week 4), may be eligible to enroll in a subsequent extension study in which they will receive open-label treatment with dupilumab.

In order to remain eligible for the OLE study, patients are required to adequately complete the assessments scheduled for the single-dose treatment and PK sampling period (through week 4) in part A, per the schedule of events described in Table 1.

For Patients Enrolled in Part B

Patients who complete the treatment period (week 16) will be offered an opportunity to screen for the OLE study at EOT visit. These patients should complete the EOT visit (as per Table 2) before screening for the OLE. Patients who discontinued prematurely (ie, patients who did not complete the protocol-defined EOT visit) cannot be screened for the OLE study before the date when the EOT visit (week 16) would have normally occurred. In order to remain eligible for the OLE study, patients are required to adequately complete the assessments scheduled in the treatment period in part B, per the schedule of events described in Table 2.

Patients who decline to participate in the OLE study will have a 12-week follow-up period.

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 (Part A), and Table 2 (Part B).

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

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.

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																							

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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																						

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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

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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**		
Efficacy[10]:																								
Assessment of Pruritus (worst scratch/itch) NRS[11,12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Skin Pain NRS and Sleep Diary[12,26]			X	X	X		X												X			X		
IGA, EASI, SCORAD, BSA, GISS	X		X	X	X		X				X				X				X	X	X	X	X	X
CDLQI[12, 13] IDQOL[12, 13, 14, DFI[12, 13] POEM[12, 14] Caregiver Missed Workdays	X		X		X		X				X				X				X	X	X	X	X	X
CGID	X		X		X		X				X				X				X	X	X	X	X	X
CGIC					X		X				X				X				X	X	X	X	X	X
PASQ[12,14,28]	X		X				X												X			X	X	X
CNSQ[12,14,29]			X				X												X			X		
Photograph AD Areas (Selected Study Sites only)			X																X			X		X

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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**		
Safety:																								
Weight	X		X																X			X		X
Height	X																		X			X		X
Vital Signs	X		X[15]	X	X		X[15]				X[15]				X				X	X	X	X	X	X
Physical Examination	X		X																X			X	X	X
ECG[27]	X																		X			X	X	X
Adverse Events[33]	X	X	X[15]	X	X	X	X[15]	X	X	X	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[16]:																								
Hematology	X						X												X			X	X	X
Blood Chemistry	X						X												X			X	X	X
HIV, HBsAg, HBsAb, HBcAb, Hepatitis C Ab, TB[17]	X																							
Serum sample for vaccination response[18]		X	X	X	X		X				X				X				X	X	X	X	X	X
Biomarkers[19]:																								
TARC			X				X												X			X		X
Serum Immunoglobulin profiling, antigen-specific IgE			X																X			X		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**		
Research Testing[25]:																								
Optional DNA buccal sample[2]			X																					
Optional tape stripping sample[31]			X																X					
PK/Drug Concentration and ADA Samples[25]:																								
PK/Drug concentration sample[19]			X				X				X				X				X	X		X	X	X
ADA sample[20]			X																X			X	X	X

Note: AD = atopic dermatitis; ADA = anti0drug antibody; AESI=adverse event of special interest; BL = Baseline; BSA = body surface area; CDLQI = Childrens' Dermatology Life Quality Index; CGIC = Caregiver Global Impression of Change; CGID = Caregiver Global Impression of Disease; CNSQ = Caregiver-Reported Nasal Symptom Questionnaire; DFI = Dermatitis Family Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; e-diary = electronic diary; EOT = End of treatment; EOS = End of Study; ET = Early Termination; GISS = Global Individual Signs Score; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; IDQOL = Infants' Dermatology Quality of Life Index; IGA = Investigator Global Assessment; IgE = immunoglobulin E; NRS = numeric rating scale; PASQ = Pediatric Asthma Symptom Questionnaire; PK = pharmacokinetic; POEM = Patient Oriented Eczema Measure; PV = phone visit; Q4W = every 4 weeks; SCN = screening; SCORAD = SCORing Atopic Dermatitis; TARC = thymus and activation regulated chemokine; TB = tuberculosis; TCS = topical corticosteroid; Std = standardization.

1 The site will contact the parent/caregiver by telephone to conduct these visits.

2 For patients whose 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.

3 Parents/caregivers of patients will be encouraged to provide vaccination plans for any vaccines which are in line with the patient's age, and local medical practice (live attenuated vaccines are excluded) during the study. Parents or legal guardians of patients planning to receive any vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples (a pre-vaccine and post-vaccine sample) for assay of vaccine IgG in serum for each vaccination.

4 The study team on site will collect information from the parents/caregivers regarding the vaccinations planned during the next 6 months from screening. The study team should refer to the patient's medical records and national vaccination schedule to gather this information. The study team can also contact the patient's primary physician and/or pediatrician to gather this information.

[5] Training of parents/caregivers regarding completion of e-diary at visit 1 to record a) completion of assessment of pruritus NRS (worst scratch/itch scale), skin pain NRS, sleep diary, and CNSQ and b) TCS and emollient usage. Provide additional training as necessary based on review of e-diary use.

[6] As per the standardized regimen outlined in Section 5.2 of the study protocol.

[7] 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.

[8] The dose regimens, including frequency of administration in part B are placebo Q4W or dupilumab Q4W tiered fixed-dose (200 mg for patients ≥5-<15kg or 300 mg for patients ≥15-<30 kg).

[9] Patients will be monitored at the study site at visits 3, 7 and 11 for a minimum of 2 hours after study drug administration.

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

[11] The assessment will be recorded daily. Parents/caregivers will complete an e-diary daily to record pruritus (worst scratch/itch) NRS in patients.

[12] The questionnaires will be administered only to those patients and/or parents/caregivers who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries). It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study.

[13] Childrens' Dermatology Life Quality Index (CDLQI) for patients ≥4 years of age, Infants' Dermatitis Quality of Life Index (IDQOL) for patients <4 years of age, Dermatology Family Index (DFI) to be completed by an adult family member of a child affected by dermatitis.

[14] Questionnaire will be completed by the parent/caregiver on behalf of the patient. It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study.

[15] Patients will be monitored at the study site at visits 3, 7, and 11 for a minimum of 2 hours after study drug administration. Vital signs (sitting systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) and AE assessments will be done at 30 minutes (±10 minutes) post-injection, and then at 2 hours (±15 minutes) post-injection.

[16] Samples will be collected before the injection of study drug.

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

[18] Optional collection of blood for assay of vaccine IgG in serum for each vaccine administered. The first sample should be drawn within 6 weeks prior to vaccination, and the second sample should be drawn 3 to 4 weeks (maximum 6 weeks) after vaccination. Vaccinations should be performed in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, samples can also be drawn at unscheduled visits.

[19] Samples to measure functional dupilumab concentration and biomarkers will be collected prior to injection of study drug.

[20] Samples to 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 may be asked to return to the clinic to have additional samples collected for analysis.

[21] The specific assessments that will be performed at the unscheduled visit will depend upon the reason for the unscheduled visit. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional PK and ADA samples may be collected at or near to the event as practically possible.

[22] Eligibility based on age at time of screening visit.

[23] Assent collected from patient, if applicable, as per local regulatory (competent authority/ethics) guidelines, based upon the age and level of maturity of the patient.

[24] The length of the screening period is not fixed but must not exceed 56 days (including TCS standardization). The length of the TCS standardization period is fixed at 14 days.

[25] 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), or vaccine response, as well as to investigate unexpected AEs or to identify markers associated with adverse reactions.

[26] Pain and sleep will be assessed daily for the 14 days leading up to the baseline visit, the 7 days leading up to the week 1 visit, the 7 days leading up to the week 2 visit, the 7 days leading up to the week 4 visit, the 7 days leading up to the week 16 visit, and 7 days leading up to the week 28 visit. Parents/caregivers will complete a daily e-diary on these days to record skin pain and sleep in patients.

[27] ECGs should be conducted prior to collection of blood samples at visits requiring blood draws.

[28] Completed only for the subset of patients with ongoing asthma.

[29] Completed only for the subset of patients with a medical history of allergic rhinitis. Caregivers will be instructed on using the e-diary to record the CNSQ for 14 days before baseline/day 1 and for the 7 days preceding visits 7, 19, and 22 (weeks 4, 16, and 28).

[30] Optional parental informed consent for use of photographs for educational/marketing purposes (selected study sites only).

[31] An optional tape stripping sub-study may be performed at a subset of study sites. Parents or legal guardians who agree for their child to participate in the 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.

[32] 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 (see Section 6.2.3.6). Any baseline findings will be documented as part of the patient's medical history and/or physical exam, as appropriate.

[33] Any patient who experiences an AESI related to an eye disorder will be referred to an ophthalmologist (see Section 7.2.3).

6.1.1. Early Termination Visit

Patients who are withdrawn from the study will be asked to return to the clinic to complete early termination assessments, as described in Table 1 (Part A) and Table 2 (Part B).

6.1.2. 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 upon the reason for the unscheduled visit. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional PK and ADA samples may be collected at or near the event as practically possible.

6.2. Study Procedures

6.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed in parts A and B of the study for the sole purpose of determining study eligibility or characterizing the baseline population: parental or legal guardian informed consent for the study and for the optional genomic sub-study, medical history, demographics, and HIV, HBsAg, HBsAb, HBcAb, and hepatitis C antibody testing. Additionally, tuberculosis testing (will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards). 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.

In part B of the study, parental or legal guardian consent for the optional vaccine sub-study, parental/legal guardian informed consent for optional use of photographs for educational/marketing purposes (selected study sites only), parental/legal guardian informed consent for an optional tape-stripping sub-study (selected study sites only), and parent/caregiver e-diary training will also be performed at the screening/baseline visit.

For the optional vaccine sub-study in part B, patients' parents or legal guardians will be encouraged to provide vaccination plans for any vaccines which are in line with the patient's age and local medical practice (live attenuated vaccines are excluded). For patients' parents or legal guardians who agree to participate in the vaccine sub-study, 2 blood samples will be collected from each patient for assay of vaccine IgG in serum for each vaccine administered. The first sample should be drawn within 6 weeks prior to vaccination, and the second should be drawn 3 to 4 weeks (±6 weeks) after vaccination (see Table 2).

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.

6.2.2.2. 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.

6.2.2.4. Caregiver Global Impression of Disease

The CGID is an assessment instrument used by the parent/caregiver in clinical studies to rate their child's eczema symptoms during the past 7 days. An appropriate version of the CGID was being developed and tested for the study-relevant age group.

Parents/caregivers will rate their child's disease based on the 5-level scale as follows:

"Overall, how would you rate your child's eczema symptoms during the past 7 days?"

- No symptoms
- Mild
- Moderate
- Severe
- Very severe

The CGID score will be assessed at time points according to Section 6.1, Table 2 (Part B).

6.2.2.5. Caregiver Global Impression of Change

Caregiver global impression of change will be measured using a caregiver administered tool that is currently being developed and tested for the study-relevant age group.

Parents/caregivers will respond to the following question based on the 7-level scale as follows:

"Compared to before your child started the study, how would you rate his or her eczema now?"

- Much better
- Moderately better
- A little better
- No change
- A little worse
- Moderately worse
- Much worse

The CGIC is an instrument used by the parent/caregiver in clinical studies to compare their child's eczema symptoms from the beginning of the study to when they completed the assessment.

The CGIC score will be assessed at time points according to Section 6.1, Table 2 (Part B).

6.2.2.6. Caregiver Assessment of Missed Workdays

Caregivers who are employed will be asked to report the number of sick-leave days since the last study assessment. Caregivers will undergo this assessment at time points according to Section 6.1, Table 2 (Part B).

The assessment tool is provided in the investigator site binder.

6.2.2.7. Childrens' Dermatology Life Quality Index

The CDLQI is a validated questionnaire designed to measure the impact of skin disease on the QOL in children ≥4 years of age (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.

A cartoon version of the CDLQI will be administered to patients 4 to 5 years of age, with the assistance of a parent or adult "as necessary". If assistance of parent or adult caregiver is required, it is recommended that the same person assist the patient throughout the study. The cartoon version of the CDLQI uses the same text and scoring system as the original CDLQI but includes 10 color drawings of a dog illustrating the theme of each question.

To complete the questionnaire, patients need to provide responses to 10 questions (the questions focus on domains such as symptoms feelings associated with disease, the impact of the disease on leisure, school or holidays, personal relationships, sleep, and side effects of treatment for the skin disease. The instrument has a recall period of 7 days. Nine of the 10 questions are scored as follows:

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

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

The CDLQI for a patient is the sum of the score of each question with a maximum of 30 and a minimum of 0. The higher the score, the greater the impact is on the QOL. The CDLQI can also be expressed as a percentage of the maximum possible score of 30. This assessment **will only be performed in part B** at time points according to Section 6.1, Table 2 (Part B).

The CDLQI is provided in the investigator site binder.

6.2.2.8. Infants' Dermatology Quality of Life Index

The IDQOL is a validated questionnaire developed to measure the impact of skin disease on the QOL of infants and preschool children <4 years of age (Lewis-Jones 2001). The IDQOL is to be completed by the child's parent or caregiver. It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study. The questionnaire consists of 10 questions related to itching and scratching; mood of the child; how long it takes for the child to get to sleep; whether the eczema has interfered with the child's playing, swimming or participation in other family activities; problems during mealtimes; problems caused by treatment; level of comfort while dressing or undressing the child; and problems during bathing. Each question asks about the impact over the previous week and is scored on a scale of 0 (minimum impact) to 3 (maximum impact).

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

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This assessment **will only be performed in part B** at time points according to Section 6.1, Table 2 (Part B).

The IDQOL questionnaire is provided in the investigator site binder.

6.2.2.9. Dermatitis Family Index

The impact on family life has been documented in families of children with very severe AD. The DFI was the first instrument assessing the impact of having a child with AD on family QOL (Lawson 1998). The 10-item disease specific questionnaire was formed after ethnographical interviews and focus groups revealed the areas of family QOL affected by AD. The self-administered instrument is completed by an adult family member of a child affected by dermatitis. It is recommended that the same person complete the questionnaire on behalf of the patient throughout the study. The items inquire about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships and the impact of helping with treatment on the primary caregiver's life. The DFI questions are scored on a four-point Likert scale ranging from 0 to 3, so that the total DFI score ranges from 0 to 30. The time frame of reference is the past week. A higher DFI score indicates greater impairment in family QOL as affected by AD. This assessment **will only be performed in part B** at time points according to Section 6.1, Table 2 (Part B).

The DFI questionnaire is provided in the investigator site binder.

6.2.2.10. Patient-Oriented Eczema Measure

An observation reported outcome (ObsRO) version of the POEM was developed simultaneously with the patient reported outcome (PRO) version and will be used here. The ObsRO version is identical to the PRO version except that it asks about "your child's skin" rather than "your skin".

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

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

The IGA is provided in the investigator site binder and in Appendix 3.

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

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.

6.2.2.19. 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.

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).

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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.

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.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. 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 pre-existing condition that is temporally associated with the use of the study drug.

7.1.2. 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 a hospital admission (any duration) or an emergency room visit 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 7.2 for more information on recording and reporting SAEs.

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.

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. Statistical Methods

The analyses for parts A and B will be performed separately.

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

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

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group for parts A and B, respectively.

9.5.2. Efficacy Analyses

For part A, the open-label portion of the study, descriptive statistics of the efficacy endpoints will be summarized.

For part B, the efficacy analysis will be performed for the comparisons between the dupilumab treatment group and the placebo group.

9.5.2.1. Primary Efficacy Analysis

The Cochran-Mantel-Haenszel test adjusted by randomization strata (region/country, baseline disease severity, and baseline weight group) will be used for the percentage of patients with IGA 0 or 1 at week 16, or percentage of patients with EASI-75 at week 16.

To account for the impact of rescue treatment on the efficacy effect: For the primary efficacy endpoints (which are binary efficacy endpoints), if rescue treatment is used (see Section 5.3), the patient will be specified as a non-responder from the time the rescue is used.

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

Sensitivity analysis will be conducted to assess the robustness of the primary efficacy analysis with regards to the handling of missing data, such as using the last observation carried forward (LOCF) approach or worst observation carried forward (WOCF) approach to determine patient's status at week 16. Details will be specified in the SAP.

In addition, the Cochran-Mantel-Haenszel method adjusted by randomization strata will also be performed on all observed data regardless if rescue treatment is used. Patients with missing data will be counted as non-responders.

9.5.2.2. Secondary Efficacy Analysis

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

For continuous endpoints, an analysis of covariance (ANCOVA) model will be used for the FAS with treatment group, randomization stratification factors (region/country, baseline disease severity, and baseline weight group) and relevant baseline measurement included in the model.

Similarly, to account for the impact of rescue treatment on the efficacy effect, patients' efficacy data through week 16 after the rescue treatment use will be set to missing. The missing data for continuous endpoints will be imputed by the pattern-mixture approach where the WOCF approach will be used for the missing due to rescue treatment, AE, and lack of efficacy and the multiple imputation (MI) approach will be used for the missing due to other reasons. The MI Statistical Analysis Software (SAS) procedure with Markov Monte Carlo algorithm will be applied for multiple times. The complete datasets created based on the pattern-mixture approach will be analyzed using the ANCOVA model defined previously, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula (Rubin, 1987).

All efficacy data will be used for analysis regardless of whether the patient is on study treatment or discontinues the study treatment but remains in the study. In addition, the MI with the ANCOVA model and the ANCOVA model based on LOCF or WOCF imputation method will be performed as the sensitivity analyses. Additional details on sensitivity analyses will be provided in the SAP.

9.5.2.3. Multiplicity Considerations

No multiplicity adjustments will be made for part A.

For part B, a hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint(s) and the secondary endpoints for the dupilumab dose regimen versus placebo. The abbreviated, preliminary plan for hierarchical testing order for the primary endpoint and key secondary endpoints is shown in Table 3. The complete hierarchy including all the secondary endpoints will be provided in the SAP.

Table 3: Preliminary Statistical Hierarchy for Multiplicity Control

	Endpoints	Dupilumab Q4W tiered fixed-dose treatment group[a]
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	1
Co-primary endpoint for EU and EU Reference Market Countries only, key secondary for US	Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16	2
Key Secondary Endpoints	Percent change in EASI score from baseline to week 16	3
	Percent change from baseline to week 16 in weekly average of daily worst scratch/itch score	4

[a] 200 mg Q4W in patients ≥5-<15 kg and 300 mg Q4W in patients ≥15-<30 kg).

9.5.2.4. Primary Analysis of the Study

In order to expedite the submission to regulatory agencies, a primary analysis may be performed when the last patient completes 16 weeks of treatment in part B. No changes in the conduct of the study will be made based on this primary analysis. The assessment of primary and secondary endpoints specified in Section 8.2.1 and Section 8.2.2 performed during the analysis will be the final analysis of the primary and secondary endpoints. Hence, there will be no need for alpha adjustment due to the primary analysis.

If a decision is made to perform the primary analysis, in order to maintain study integrity with respect to the post-treatment follow-up visits, safety visits and analyses, a dissemination plan will be written. This plan will clearly identify the unblinded team (including the statistician) that will perform the primary analysis and all related activities, restrict other clinical team members and other sponsor personnel from access to individual patient treatment allocation and site level analysis results (ie, remain blinded), and ensure that the dedicated unblinded team will not participate in the data review or data decisions for the subsequent post-treatment analyses. However, the dedicated unblinded team can participate in the analysis following the final database lock.

9.5.3. Safety Analysis

The safety analysis will be based on the SAF. This includes reported TEAEs, AESIs, and other safety information (eg, clinical laboratory evaluations, vital signs, and 12-lead ECG results). A summary of safety results for each treatment group will be presented.

9.5.3.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined separately for parts A and B:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from the first dose of study drug to the end of the study. In Part B, the treatment-emergent period includes the 16-week treatment period and follow-up period.
  - Treatment period: date of the first dose of study drug to week 16 visit date (study day 113 starting from the first dose of study drug if week 16 visit date is unavailable) or early termination date, whichever comes first.
  - Follow-up period: date after week 16 visit date (study day 113 starting from first dose of study drug if week 16 visit date is unavailable) or early termination date, to end of study. Patients who continue into the OLE after the treatment period will not have a follow-up period.

Treatment-emergent AEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the overall study period.

Analysis

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

Summaries of all TEAEs by treatment group 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.

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)

- NAb status for samples that are positive in the ADA assay

Analyses described below will be performed separately for parts A and B unless otherwise specified. Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers, and NAb positivity presented by patient, time point, and dose group will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles may be evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

9.5.6. Analysis of Biomarker Data

In parts A and B, all exploratory biomarker data analyses will be performed on the SAF and no multiplicity adjustment is planned. Analyses of blood biomarker endpoints (TARC and IgE) will be provided in the SAP and results will be presented in the final clinical study report. Analyses from tape stripping and genomics sub-studies will not be reported in the clinical study report.

9.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment in part A will be the latest valid, pre-first-dose assessment available in part A
- The baseline assessment in part B will be the latest valid, pre-first-dose assessment available in part B

General rules for handling missing data:

- Rules for handling missing data for efficacy assessments are provided in Section 9.5.2.
- 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.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with non-protocol 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.

9.7. 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 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

The CRF data for this study will be collected with an Electronic Data Capture (EDC) tool.

10.2. Electronic Systems

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

- IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Argus – a pharmacovigilance and clinical safety software system (Regeneron)
- AWARE, Business Objects XI – pharmacovigilance activities (Sanofi)

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with International Council for Harmonisation (ICH) guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited

to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

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

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

11.3. Case Report Form Requirements

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

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

12. AUDITS AND INSPECTIONS

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

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

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In

addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign.

- Parent(s) or legal guardian(s) who can write but cannot read will have the ICF read to them before writing their name on the form.
- Parent(s) or legal guardian(s) who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

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

13.3. Patient Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB/EC-approved amendment.

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

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

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A PHASE 2/3 STUDY INVESTIGATING THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF DUPILUMAB IN PATIENTS AGED ≥6 MONTHS TO <6 YEARS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS, and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: A Phase 2/3 Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab In Patients Aged ≥6 Months to <6 Years with Moderate-to-Severe Atopic Dermatitis

Protocol Number: R668-AD-1539

Protocol Version: R668-AD-1539 Amendment 4

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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

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

No:

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

Yes:

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

NOTE: This list is not exhaustive.

APPENDIX 2. PERMITTED AND PROHIBITED STEROID MEDICATION

Low potency steroids (permitted)	**Medium potency steroids (permitted as rescue, prohibited otherwise)**
Hydrocortisone acetate 1% cream / Hydrocortisone 1% cream (provided to sites by sponsor) Desonide 0.05% cream Alclometasone dipropionate 0.05% cream	Triamcinolone acetonide 0.1% ointment (provided to sites by sponsor) Triamcinolone acetonide 0.1% cream Fluticasone propionate 0.05% cream Fluocinolone acetonide 0.025% ointment
High Potency steroids (permitted as rescue, prohibited otherwise)	**Very high potency steroids (prohibited)**
Mometasone furoate 0.1% ointment Triamcinolone acetonide 0.5% ointment	Clobetasol propionate 0.05% ointment Betamethasone dipropionate 0.05% ointment

This is a representative list of TCS to be used in the study based on the American Academy of Dermatology classification (Eichenfield 2014). 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/mild potency TCS may also be used on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.). Hydrocortisone acetate 1% cream / hydrocortisone 1% cream should be used unless there are known side effects to these agents or due to non-availability due to any reason. In those cases, other low potency TCS such as desonide 0.05% cream or alclometasone dipropionate 0.05% cream can be used. The use of medium/high potency steroids should be reserved for rescue. It is recommended that triamcinolone acetonide 0.1% ointment be used for rescue. However, other medium or high potency TCS may be used as per investigator discretion. The use of very high potency steroids is not allowed during the study.

APPENDIX 3. IGA SCALE

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

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

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

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

IGA: Disease Severity Scale and Definitions of the scoring:

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

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