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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY
TO INVESTIGATE THE EFFICACY AND SAFETY OF DUPILUMAB
MONOTHERAPY IN PATIENTS ≥ 12 TO < 18 YEARS OF AGE, WITH
MODERATE-TO-SEVERE ATOPIC DERMATITIS**

Compound: Dupilumab

Clinical Phase: 3

Protocol Number: R668-AD-1526

Protocol Version: R668-AD-1526 Amendment 3

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AMENDMENT HISTORY

Amendment 3

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

Change	Section Changed
1. Moved the following endpoint from other secondary to key secondary endpoints: Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 3 from baseline to week 16 Rationale: The sponsor will conduct a post-hoc responder analysis to determine the relevant threshold for the adolescent population. The sponsor believes that an improvement in Pruritus NRS by 3 points may be clinically relevant especially in a pediatric population; hence, this endpoint has been prespecified in the protocol. 2. Added the following endpoint to the list of other endpoints: Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 3 from baseline during the 16-week treatment period Rationale: The sponsor believes that this endpoint is clinically relevant; hence, should be prespecified in the protocol. 3. Made changes to the statistical hierarchy for multiplicity control. Rationale: The order of testing for certain endpoints was re-arranged based on further internal review and discussions. This was based on review of the power calculation assumptions and the perceived clinical relevance of the endpoints.	Synopsis, Secondary endpoints Section 8.2.2 Secondary Endpoints Section 9.5.2.3 Multiplicity Considerations Table 3 Statistical Hierarchy for Multiplicity Control
Revision was made in Inclusion Criterion #8 for clarification purpose based on clarification letter previously sent to investigators, regulatory authorities, ethic committees and independent review boards.	Section 4.2.1 , Inclusion Criteria, #8
The biomarker sample type was changed from “serum/plasma” to “serum” based on clarification letter previously sent to investigators, regulatory authorities, ethic committees and independent review boards.	Table 1 Schedule of Events (Screening, Baseline, and Treatment Period) – row for Biomarker Samples Table 2 Schedule of Events (treatment Period cont, Follow-Up Period, Unscheduled Visits, and Early Termination) - row of Biomarker Samples Section 6.2.5 Biomarker Procedures

Amendment 2

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

Change	Section Changed
Added an exclusion criterion #9 of “Treatment with crisaborole within 2 weeks prior to the baseline visit.” Crisaborole was recently approved in the US for the treatment of mild to moderate AD in patients 2 years and older. This exclusion criterion has been added to ensure that patients will be completely washed off this topical therapy before baseline assessments and to minimize any carry-over effects into the treatment period. This will minimize any confounding of efficacy assessment for the study drug.	Section 4.2.2 Exclusion Criteria
Revised exclusion criteria #19: Creatine phosphokinase (CPK) >2.5× ULN to Creatine phosphokinase (CPK) >5× ULN. The criterion for temporary discontinuation of drug for elevated CPK levels (section 5.4.2.2 of protocol) has also been modified accordingly. Increases in CPK levels which are transient and not clinically significant are well known after strenuous exercise, especially in adolescent patients. Moreover, based on data gathered from studies with dupilumab in adult patients and in pediatric patients (R668-AD-1412), there is no evidence that dupilumab per se has any impact on CPK levels in blood. The drug is not expected to have such an effect based on its mechanism of action. The sponsor believes that this should be the optimal threshold which while ensuring patient safety will not be overly restrictive and not negatively impact patient recruitment and retention during the study. This would ensure that pediatric patients are not unnecessarily deprived of a potentially useful therapy for a disease with high unmet medical need.	Section 4.2.2 Exclusion Criteria Section 5.4.2.2 Reasons for Temporary Discontinuation of Study Drug
Corrected the expellable volume for 200 mg to 1.14 mL instead of 1.0 mL.	Section 5.1 Investigational and Reference Treatments
Clarified the text indicating where moisturizers should be applied by the deletion of the following text in the third sentence “on the area(s) of nonlesional skin designated for such assessments”	Section 5.2 Background Treatment
Added the medication crisaborole to the list of prohibited agents because it is a treatment for atopic dermatitis and would interfere with the efficacy evaluation. Crisaborole has been added to the list of prohibited medications to prevent any confounding of efficacy assessment for the study drug.	Section 5.7.1 Prohibited Medications and Procedures

Change	Section Changed
In original version of protocol, there were certain criterion that were needed to be met before patients could be offered roll-over into OLE at end of treatment period. Patients who did not meet these criteria would be followed up during the 12 week follow up period before they were allowed entry into OLE. In the amended version, all patients would be offered entry into OLE at end of treatment. The patients who decline OLE will be followed up for 12 weeks. The primary purpose of the 12 week follow up period was to gather off-treatment efficacy and safety data in pediatric patients. However, this provision is now built in the OLE protocol as patients who have been exposed to drug for 52 weeks, and have achieved clinical response will be taken off treatment and efficacy/safety will be observed in these patients. Moreover, seamless transition into OLE will prevent pediatric patients from developing flares of disease during the follow up period. Continuous treatment is also expected to minimize the development of ADAs due to treatment interruption.	Section 3.1 Study Description and Duration Section 5.8 Continuation of Dupilumab Treatment in an Open-Label Extension Study
Added the provision: If baseline/day 1 visit occurs within 14 days of screening, hematology and serum chemistry do not need to be repeated at the baseline/day 1 visit as long as these assessments were performed at the screening visit. This would help minimize blood volumes collected in this pediatric population.	Section 6.1 Schedule of Events, Table 1
Removed hematology and chemistry assessments at week 2 and week 12. This has been done to minimize the volume of blood collected in a pediatric population. These assessments would still be being conducted at screening, baseline, week 4, week 8, week 16, and end of study, which should be sufficient to allow detection of any clinically significant abnormality in these lab parameters within a reasonable time frame. Moreover, data from dupilumab studies in adult patients and the phase 2 study in pediatric patients (R668-AD-1412) does not suggest that dupilumab has an impact on any of the lab parameters being evaluated under serum hematology and chemistry.	Section 6.1 Schedule of Events, Table 1
Removed the Pain Assessment with Visual Analogue Scale (VAS) from phone visit 16 for accuracy.	Section 6.1 Schedule of Events, Table 2
Corrected the text related to the The Total Nasal Symptoms Score (TNSS) to state “The Total Nasal Symptom Score (TNSS) will be used to assess the effect of study drug on symptoms of allergic rhinitis. The summed score will include the following 5 4-nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, <u>and difficulty in sleeping</u> , each rated...”	Section 6.2.2.9 – Total Nasal Symptom Score
Added the Investigator’s Global Assessment (IGA) scale to the protocol. The scale was already included in the efficacy procedures and in the Study Manual and was added to Appendix 2 for further clarification.	Section 6.2.2.11 Investigator’s Global Assessment

Change	Section Changed
Added that the investigator will also assess whether the AES are related to any study procedures (as listed in Tables 1 and 2). This will allow better characterization of adverse events during the study. Deleted the heading “Relationship of AEs to Study Drug” since the section is also referring to relationship to procedures.	Section 7.3.2 Evaluation of Causality
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
As per FDA request, added that The Mantel-Fleiss (MF) criterion will be performed, and if it is not met while using the option CMH (MF) in SAS procedure PROC PREQ, sensitivity analyses including each factor separately in CMH test will be conducted. This methodology was added to further clarify the testing.	Section 9.5.2.1 Primary Efficacy Analysis Synopsis (Statistical Plan)

Change	Section Changed
As per FDA request, provided further details on the methodology for multiple imputation of the continuous endpoints and deleted text related to missing data from the FAS. For continuous endpoints, added that the multiple imputation (MI) with analysis of covariance (ANCOVA) model will be used “as the primary analysis method.” Added the following text to clarify the methodology: “Patients’ efficacy data through week 16 after the rescue treatment use will be set to missing first, and then be imputed by the multiple imputation method. Missing data from the FAS will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI following the 2 steps below: Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345. Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates including treatment groups, randomization strata (disease severity, weight group), and relevant baseline. The week 16 data of each of the 40 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (disease severity, weight group), and relevant baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin’s formula.” Deleted the following text: “Missing data from the FAS will be imputed multiple times to generate a complete dataset at each imputation by using the MI Statistical Analysis System (SAS) procedure. These complete datasets will be analyzed using an ANCOVA model with treatment, randomization strata (baseline disease severity and weight group) and relevant baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin’s formula.”	Section 9.5.2.2 Secondary Efficacy Analysis Synopsis (Statistical Plan)

Change	Section Changed
As per FDA request, added the hierarchy for testing procedures for primary and secondary endpoints across the two dupilumab dose regimens to further clarify the testing. The following text was added: “The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens versus placebo. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in below table (all comparisons are with the placebo).” The following text was deleted: “A hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens vs placebo. The hierarchy of testing procedure will be provided in the SAP.” Added an endpoint table to clarify the statistical changes for the Primary endpoint, Co-primary endpoint for ex-US countries, key secondary for US, Key Secondary endpoints, and Secondary Endpoints.	Section 9.5.2.3 Multiplicity Considerations Synopsis (Statistical Plan)
Minor editorial changes	Section 5.4.2.1 Reasons for Permanent Discontinuation of Study Drug

AMENDMENT 1

NOTE: This is the first version of the protocol that will be implemented.

The objectives of amendment 1 are to:

- Add a 200 mg every 2 week (Q2W) regimen (with a loading dose of 400 mg on day 1) to the Q2W treatment group. Patients below 60 kg will receive 200 mg Q2W, while patients ≥ 60 kg will receive 300 mg Q2W (with a loading dose of 600 mg on day 1). This weight-adjusted dosing better fulfills the conventional therapeutic objective to utilize the minimum effective dose. This tiered weight-based approach will reduce difference in exposure levels between patients with different body weights. In addition, it will allow assessment of a dose regimen that involves injection of lower volume of drug product (1 mL). A lower volume injection may be better tolerated by pediatric patients.
- Increase sample size from 180 patients to 240 patients. Assumptions for power calculations in the original protocol were based on phase 2b trial in adults. Since then, results from Phase 3 trials in adults (SOLO) have become available in which a higher placebo response was seen. Accordingly, assumptions for power calculations were updated and an increase in sample size is required to keep the study adequately powered for the primary endpoint (Proportion of patients achieving IGA 0/1). Increasing the sample size will enable a more rigorous assessment of the therapeutic profile of dupilumab in this patient population.
- Change duration of treatment period from 12 weeks to 16 weeks. The treatment duration was increased to enable detection of maximum therapeutic effect of dupilumab and maximize the likelihood to detect a statistically significant difference versus placebo on the primary endpoint. The study design was originally informed by results from adult phase 2b trial (study R668-AD-1021), which suggested efficacy of dupilumab had plateaued at week 12 with no incremental efficacy between week 12 and week 16. However, recently available results from phase 3 studies in adults showed an increase in efficacy for dupilumab treatment arms between week 12 and week 16.
- Revise the fourth bullet point under inclusion criterion number 8 from "... If documentation is inadequate, potential patients may be rescreened after such documentation is obtained (ie, patients are shown to fail a 28-day course of mid-to-higher potency TCS [$\pm$ TCI])" to "... If documentation is inadequate, potential patients may be offered a course of treatment with a daily regimen of TCS of medium or higher potency ($\pm$ 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 during this period, as defined above, will be eligible for inclusion in the study, following appropriate washout". The language in original protocol was ambiguous as it suggested that all patients were to be re-screened if they were offered a course of TCS to demonstrate inadequate response. However, there might be some patients who would be able to enroll into the study as part of the initial screening as

long as they are able to complete the course of TCS within the screening period of 35 days. The revised text serves to clarify this ambiguity.

- Revise inclusion criterion number 11 from “Patient either alone or with the help of their parents/legal guardians, as appropriate, must be able to understand and complete study-related questionnaires” to “Able to understand and complete study-related questionnaires”. The objective of making this change is to ensure that patient reported outcome questionnaires are completed by patients alone, as assistance from parents or caregivers might bias the interpretation and response to questions in the instrument.
- Revise exclusion criterion number 2 from “Treatment with an investigational drug before the baseline visit” to “Treatment with a systemic investigational drug before the baseline visit”, and add another exclusion criterion (criterion number 3) in this context: “Treatment with a topical investigational drug within 4 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit”. The previous exclusion criterion was too restrictive and would have prevented patients who had received topical investigational agents for AD, at any time prior to screening visit, from being enrolled in this study. The updated exclusion criterion enables such patients to be enrolled in this trial, conditional upon a 4-week or a period of 5-half-lives washout for the topical investigational agent.
- Revise exclusion criterion number 4 (old criterion number 3 in the original protocol) from “Treatment with TCS or topical calcineurin inhibitors (TCI) within 1 week before the baseline visit (patients may be rescreened)” to “Treatment with TCS or topical calcineurin inhibitors (TCI) within 2 weeks before the baseline visit (patients may be rescreened)”. The duration of a washout period for TCS and TCIs has been increased to 2 weeks to ensure that patients are completely washed off these topical therapies before baseline assessments and to prevent any carry-over effects from these agents into the treatment period.
- Revise exclusion criterion number 12 (old criterion number 11 from the original protocol) from “Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the screening visit, or superficial skin infections within 1 week before the screening visit” to “Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the baseline visit”. The objective of this exclusion criterion in the original protocol was to prevent patients with active infections from receiving the study drug and to allow a sufficient duration between the resolution of infection and first administration of study drug. Since first administration of study drug will take place at baseline and not screening, the baseline visit and not the screening visit is the relevant reference time point for the purpose of implementation of this criterion. Data from the phase 3 program in adults has shown that dupilumab actually reduces the risk of superficial skin infections. Hence, the exclusion criterion around superficial skin infections was removed.

- Change exclusion criterion number 18 (old criterion number 17 from the original protocol) to exclude patients with laboratory abnormalities at screening consistent with Common Terminology Criteria for Adverse Events (CTCAE) grade 2 and above. Changes were made to the exclusionary values for neutrophil count (previously $<1000/\mu\text{l}$, revised $<1500/\mu\text{l}$), serum creatinine value (previously 2mg/dl , revised $>1.5\text{ ULN}$) and serum creatine phosphokinase (CPK) level (previously $>10\text{ ULN}$, revised 2.5 ULN) at screening. The criteria for temporary discontinuation of study drug due to laboratory abnormalities were updated to be consistent with the exclusion criteria. This change has been made to address a regulatory agency request to make the exclusion criterion around lab parameters more stringent.
- Revise exclusion criterion number 22 (old criterion number 21 from the original protocol) from “History of alcohol or drug abuse within 2 years before the screening visit” to “History of alcohol or drug abuse within 2 years before the screening visit or evidence of such abuse as documented by a positive result in laboratory test of alcohol and/or drug panel conducted at screening”. Excluding patients on basis of an objective lab test will be a more reliable way to assess ongoing alcohol or drug use.

Also, added a clarifying note that patients who have a positive drug test due to a prescription drug being used for medical reasons, will still be eligible for enrollment into the study.

- Revise the schedule of events:
 - Add a blood sample at week 4, visit 6 for assessment for anti-drug antibody (ADA) to Table 1. This change has been made based on a Health Authority request. It will allow further characterization of the immunogenicity of the study drug.
 - Add injection training/observation at week 12, visit 14 to Table 1
 - Add “Assess missed school days” assessment to Table 1 and Table 2. This patient reported outcome allows evaluation of effect of study drug on school related productivity.
 - Add “Total Nasal Symptom Score (TNSS)” assessment to Table 1 and Table 2 and add footnote “k” to Table 1 and footnote “h” to Table 2 to state that “TNSS will be administered only to patients with medical history of allergic rhinitis throughout the screening period (at least 7 days before baseline/day 1) and only for 7 days preceding visit 6, visit 18 (EOT), and visit 21 (EOS).” This patient reported outcome allows evaluation of effect of study drug on symptoms of Allergic Rhinitis, a commonly seen co-morbidity in patients with AD.
 - Add “Patient Assessment of Injection Pain Using Visual Analogue Scale (VAS)” assessment to Table 1 and Table 2. This patient reported outcome enables evaluation of tolerability of dupilumab injections in an adolescent population.
 - Add “Patient/parent(s) or caregiver paper diary training for dosing” to Table 1 and add “Review home diary” to Table 1 and Table 2

- Revise footnote “g” of Table 1 and footnote “d” of Table 2 to further clarify that at “in-clinic visits, sites will perform accountability assessment for the study drug that the patients or parents/caregivers have returned to the site.”
- Remove SNOT questionnaire from Table 1 and Table 2 and delete from footnote “j” of Table 1 and footnote “e” of Table 2 that SNOT-22 will be administered only to patients with a history of chronic (rhino) sinusitis or nasal polyps.
- Revise footnote “h” of Table 1 and footnote “e” of Table 2 to clarify that patient-reported assessments are to be completed only by the patient.
- Revise footnote “j” of Table 1 and footnote “g” of Table 2 to clarify that ACQ-5 will only be administered to patients with on-going asthma (in the original protocol, ACQ-5 was planned in patients with medical history of asthma).
- Add “Study drug administration” and “Patient dosing paper diary completion” at week 14, visit 15 to Table 2.
- Rename “Research samples (serum/plasma)” to “Biomarker samples (serum/plasma)” and move under Biomarker (Table 1 and Table 2). [REDACTED]
- Add that “Samples positive in the ADA assay will be analyzed in the Neutralizing antibody (NAb) assay.” to footnote “c” of Table 2.
- Remove the endpoint hierarchy under Multiplicity Considerations; details will be specified in the SAP.
- Include a description of the possible first-step analysis
- Make the following change to the list of “Primary Endpoints”:
 - Update all endpoints previously being assessed at 12 weeks to be assessed at 16 weeks (to align with increase in duration of treatment period from 12 weeks to 16 weeks).
- Make the following changes to the list of “Secondary Endpoints”:
 - Update all endpoints previously being assessed at 12 weeks to be assessed at 16 weeks (to align with increase in duration of treatment period from 12 weeks to 16 weeks)
 - Rearrange the order of the key secondary endpoints
 - Add the following endpoint:
 - Percent change in EASI score from baseline to week 16

- Revise the following endpoints (to harmonize with adult phase 3 trials):
 - “Percent change from baseline to week 12 in Pruritus Numerical Rating Scale (NRS)” to “Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS”
 - “Proportion of patients with improvement (reduction) of Pruritus NRS ≥ 4 from baseline to week 12” to “Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 16”
 - “Proportion of patients with improvement (reduction) of Pruritus NRS ≥ 3 from baseline to week 12” to “Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 3 from baseline to week 16” AND move this endpoint to the list of “Other Secondary Endpoints”
- Make the following changes to the list of “Other Secondary Endpoints”:
 - Update all endpoints previously being assessed at 12 weeks to be assessed at 16 weeks (to align with increase in duration of treatment period from 12 weeks to 16 weeks)
 - Rearrange the order of other secondary endpoints
 - Change all "pruritus NRS" to "peak pruritus NRS"
 - Add the following endpoints:
 - Change from baseline to week 16 in weekly average of daily peak Pruritus NRS
 - Proportion of patients with EASI-50 at week 16
 - Proportion of patients with EASI-90 at week 16
 - Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline during the 16-week treatment period
 - Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 4
 - Incidence of skin-infection treatment-emergent adverse events (TEAEs) (excluding herpetic infections) through week 16
 - Incidence of serious treatment-emergent adverse events (TEAEs) through week 16
 - Remove the following endpoint: Proportion of patients with SCORing Atopic Dermatitis (SCORAD)-50 ($\geq 50\%$ reduction in SCORAD from baseline) response at week 12

- Remove the following endpoint: Change from baseline to week 12 in Global Individual Signs Score (GISS; erythema, infiltration, papulation, excoriations, lichenification)
 - Revise the following endpoints:
 - “Percent change in EASI score from baseline to week 12” to “Percent change in EASI score from baseline to week 16” AND move this endpoint to the list of “Key Secondary Endpoints”
 - “Percent change from baseline to week 2 in Pruritus NRS” to “Percent change from baseline to week 4 in weekly average of daily peak Pruritus NRS”
 - Removed the list of “Other Endpoints and Assessments” and noted that these will be specified in the Statistical Analysis Plan (SAP), as applicable.
 - Revise the number of imputations used to generate a complete data set for missing data from the full analysis set (FAS) from 50 times to multiple times.
 - Add a description of the power calculations based on the key secondary endpoint “Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 16”
 - Add language to section 9.5.2.1 “Primary Efficacy Analysis” to clarify that data collected after study drug discontinuation will also be used in all analyses.
 - Correct the IND number
 - Add that “Regulatory approvals will also be obtained where required by local legislation.”
 - Update the Introduction to include more current information about completed and ongoing trials in the dupilumab program
 - Update reasons for temporary discontinuation of study drug
 - Make the following changes to section 5.8 “Continuation of Dupilumab Treatment in an Open-Label Extension Study”:
 - Remove the first bullet point “Patients have completed at least 6 weeks of study treatment and the remaining assessments during the treatment period (through week 12)” and replace with, “The patient needs to have completed at least 5 on site visits (including completing the study assessments and procedures planned for each of those visits), during the 16-week treatment period.
- AND
- The patient needs to have completed at least 6 study drug administrations during the 16-week treatment period.”
- Clarify that the screening visit for the open-label extension may be completed on the same day as the early termination visit

- Revise the requirement of BSA affected by AD lesions from >10% to $\geq 10\%$
- Clarify that patients who experience a flare during the follow-up period and would otherwise require treatment with systemic corticosteroids or immunosuppressive drugs can be directly enrolled into the open-label extension study at the investigator's discretion.
- Clarify that study drug administration refers to injections of dupilumab or placebo.
- Clarify that patients will be trained at screening and baseline on using diaries to record Pruritus NRS score, pruritus categorical scale score, assessment of Total Nasal Symptom Score (TNSS), and emollient usage, and at visit 6/week 4 on using a paper diary to record administration of each dose of study drug outside the clinic
- Add language to section 6.2 "Study Procedures" indicating the order in which assessments/procedures should be performed at study visits
- Revise the list of AESIs. 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.
- Revise the Biomarker Procedures section to align with the new procedures for collection, use, and storage of biomarker serum and plasma samples [REDACTED]
[REDACTED]
- Revise the definition of concomitant medications and procedures
- Delete the section on Cytochrome P450. Data became available recently from a phase 1 study to examine the Effects of Dupilumab on the Pharmacokinetics of Selected Cytochrome P450 Substrates in Adult Patients with Moderate to Severe Atopic Dermatitis. The results of this study showed no evidence for a clinically meaningful effect of dupilumab on the PK of a cocktail of prototypic substrates, indicating that blockade of IL4/13 signaling does not have a clinically relevant effect on the activity of CYP3A, CYP2C19, CYP2C9, CYP1A2 or CYP2D6, in adult patients with moderate to severe AD.
- Revise the definition of "total number of patients with treatment-emergent ADA response in ADA assay" from "total number of patients with treatment-emergent ADA response in ADA assay – defined as either a positive response in ADA assay postbaseline when baseline results are negative, or any postbaseline positive response in ADA assay with a titer ≥ 4 -fold over the baseline titer level." to "total patients with treatment-emergent response – defined as a positive response in the ADA assay post first dose when baseline results are negative or missing". This change was made to harmonize with the definition used for ADA analysis performed in phase 3 adult studies.

- Revise the definition of “persistent ADA response” from “a treatment-emergent ADA positive response with 2 or more consecutive positives in the ADA assay separated by at least a 12-week period” to “a treatment-emergent ADA positive response with 2 or more consecutive ADA positive sampling time points, separated by greater than a 12-week period (with no ADA negative samples in between)”. This change was made to harmonize with the definition used for ADA analysis performed in phase 3 adult studies.
- Clarify the definition of the ADA analysis set from “all treated patients who received any study drug and who had at least 1 qualified result in the ADA assay after the first dose of the study drug” to “all treated patients who received any study drug and who had at least 1 non-missing reportable ADA result (either “ADA negative” or “ADA positive”) after first dose of the study drug”. This change was made to harmonize with the definition used for ADA analysis performed in phase 3 adult studies.
- Include that ADA positive samples will be further characterized for the presence of neutralizing antibody response
- Clarify that ADA variables will be summarized using descriptive statistics by treatment groups
- Make editorial changes for clarity and consistency

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY IN PATIENTS ≥ 12 TO < 18 YEARS OF AGE, WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS
Site Locations	Multiple sites in North America; other regions may be included.
Principal Investigator	To be determined
Objectives	The primary objective of the study is to demonstrate the efficacy of dupilumab as a monotherapy in patients ≥ 12 years to < 18 years of age with moderate-to-severe atopic dermatitis (AD). The secondary objective of the study is to assess the safety of dupilumab as a monotherapy in patients ≥ 12 years to < 18 years of age with moderate-to-severe AD.
Study Design	This is a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of dupilumab monotherapy in pediatric patients with moderate-to-severe AD. The study population will include patients ≥ 12 years to < 18 years of age with 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). Approximately 240 study patients are planned to be randomized to 1 of the following treatment groups: • Dupilumab every 2 weeks (Q2W) treatment group: 200 mg Q2W (patients < 60 kg) or 300 mg Q2W (patients ≥ 60 kg) • Dupilumab every 4 weeks (Q4W) treatment group: 300 mg Q4W, irrespective of weight • Placebo group The study will consist of the following 3 periods: screening of up to 5 weeks, treatment period of 16 weeks, and follow-up of 12 weeks. After the parents or legal guardians/patients provide informed consent and informed assent (as appropriate), the patients will be assessed for study eligibility at the screening visit. During the screening period, systemic and topical treatments for AD will be washed out, as applicable, according to the eligibility requirements. Patients may be rescreened once 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 and continue throughout the study.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio stratified by baseline weight group (<60 kg and ≥ 60 kg; each weight stratum will enroll approximately 120 patients) and baseline disease severity (moderate [Investigator's Global Assessment (IGA=3)] vs. severe [IGA=4] AD) as follows:

- Dupilumab Q2W treatment group: Patients with baseline weight <60 kg will receive Q2W subcutaneous (SC) injections of 200 mg dupilumab following a loading dose of 400 mg on day 1. Patients with baseline weight ≥ 60 kg will receive Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Dupilumab Q4W treatment group: Patients will receive Q4W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Placebo treatment group: Patients will receive placebo matching dupilumab Q2W (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, patients in the <60 kg weight stratum will receive, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥ 60 kg weight stratum, the patients randomized to the placebo group will receive placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

In order to maintain blinding, all patients will receive an injection Q2W from day 1 to week 14. Patients will receive placebo injection at the weeks dupilumab is not given.

During the treatment period, patients will have weekly in-clinic visits through week 4, then every 4 weeks in-clinic visits through week 16, with weekly telephone visits in between in-clinic visits. Patients and/or parents/caregivers (as deemed appropriate based on age of patient) will be trained on injecting study drug during in-clinic visit 2 (day 1) to visit 6 (week 4). During weeks in which no in-clinic visit is scheduled, patients will either self-inject study drug or the parent/caregiver will administer study drug to the patient. In case patients do not want to self-inject and the parent/caregiver do not want to administer study drug to patient, patients may have the clinic staff administer all the study drug injections in the clinic. Safety, laboratory, and clinical assessments will be performed at specified clinic visits. The end of treatment period visit will occur at week 16, two weeks after the last dose of study drug. The co-primary endpoints will be assessed at this visit.

Patients who participate in the study may subsequently be eligible to participate

	in an open-label extension study.
Study Duration	The duration of the study for each patient is approximately 28 weeks, excluding the screening period.
Population	
Sample Size:	Approximately 240 patients are planned to be enrolled into 3 groups (80 per group): dupilumab Q2W treatment group (200 mg Q2W or 300 mg Q2W), dupilumab Q4W treatment group (300 mg Q4W), or placebo group.
Target Population:	The study population includes pediatric patients (aged ≥ 12 to <18 years at the time of baseline) who have moderate-to-severe AD that cannot be adequately controlled with topical AD medications or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects or safety risks).
Treatments	
Study Drug	Dupilumab will be given every other week or every 4 weeks:
Dose/Route/Schedule:	• Dupilumab Q2W treatment: - o SC injections of dupilumab, 400 mg loading dose on day 1, then 200 mg Q2W from week 2 to week 14, or - o SC injections of dupilumab, 600 mg loading dose on day 1, then 300 mg Q2W from week 2 to week 14 • Dupilumab Q4W treatment: SC injections of dupilumab, 600 mg loading dose on day 1, then 300 mg Q4W from week 4 to week 12; in order to maintain the blind, there will be an SC injection of placebo in between dupilumab doses during the week 2 to week 14 dosing period so the injection frequency will match the other 2 groups.
Placebo	Matching placebo
Route/Schedule:	SC injections of placebo matching dupilumab Q2W (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, patients in the <60 kg weight stratum who are randomized to the placebo group will receive, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).
Background Treatment	All patients are required to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization. After randomization, patients are required to continue to apply moisturizers throughout the study (all 28 weeks where applicable). However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of

nonlesional skin designated for such assessments for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers 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.

Endpoints

Primary (for US):

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

Co-primary (for ex-US countries):

- Proportion of patients with Eczema Area and Severity (EASI)-75 ($\geq 75\%$ improvement from baseline) at week 16
- Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16

Secondary:

Key Secondary Endpoints:

- Proportion of patients with EASI-75 ($\geq 75\%$ improvement from baseline) at week 16 (this is not a secondary endpoint for ex-US countries as it is already a co-primary endpoint)
- Percent change in EASI score from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 3 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 16

Other Secondary Endpoints:

- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Time to onset of effect on pruritus during the 16-week treatment period (≥ 3 point reduction of weekly average of peak Pruritus NRS from baseline)
- Time to onset of effect on pruritus during the 16-week treatment period (≥ 4 point reduction of weekly average of peak Pruritus NRS from baseline)
- Change from baseline to week 16 in percent body surface area (BSA) affected by AD
- Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)
- Change from baseline to week 16 in Children's Dermatology Life Quality Index (CDLQI)
- Change from baseline to week 16 in Patient Oriented Eczema Measure

(POEM)

- Change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Percent change from baseline to week 4 in weekly average of daily peak Pruritus NRS
- Change from baseline to week 16 in Hospital Anxiety and Depression Scale (HADS)
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 4
- Incidence of skin-infection treatment-emergent adverse events (TEAEs) (excluding herpetic infections) through week 16
- Incidence of serious TEAEs through week 16

Procedures and Assessments

Efficacy will be assessed during the study at specified clinic visits using investigator-reported assessments (including IGA that rates the overall severity of AD, EASI that measures the extent and severity of AD, SCORAD, BSA affected by AD, and GISS). In addition, patient-reported assessments (including Pruritus NRS, Pruritus PCS, patient global assessment of disease, patient global assessment of treatment, CDLQI, POEM, HADS, 5-question version of Asthma Control Questionnaire [ACQ-5], Total Nasal Symptom Score [TNSS], patient assessment of injection pain using Visual Analogue Scale [VAS], and patient assessment of missed school days [for patients who are enrolled in school]) will be used to assess their related endpoints.

Safety will be assessed by vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and clinical evaluations. Patients will be asked to monitor all adverse events (AEs) experienced from the time of informed consent/assent until their last study visit.

Statistical Plan**Sample size Consideration:**

It is estimated that with 80 patients per group, at the 2-sided 5% significance level, the study will have:

- 98% power to detect a difference of 28% between dupilumab Q2W and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at week 16, assuming that the percentages are 37% and 9% for dupilumab Q2W and placebo, respectively.
- 88% power to detect a difference of 20% between dupilumab Q4W treatment and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at week 16, assuming that the percentages are 29% and 9% for dupilumab Q4W and placebo, respectively.
- 99% power to detect a difference of 35% between dupilumab Q2W treatment and placebo treatment in the percentages of patients achieving EASI-75

response at week 16, assuming that the percentages are 48% and 13% for dupilumab Q2W and placebo, respectively.

- 99% power to detect a difference of 32% between dupilumab Q4W treatment and placebo treatment in percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 45% and 13% for dupilumab Q4W and placebo, respectively.

Additional power calculation based on the key secondary endpoint “proportion of patients with improvement (reduction) of Pruritus NRS ≥ 4 from baseline to week 16”, with 80 patients per group, the study will provide:

- 97% power at a 0.05 level to detect a difference of 27% in the percentages of patients achieving Pruritus NRS reduction ≥ 4 at week 16, assuming that the percentages are 38% and 11% for dupilumab Q2W and placebo, respectively.
- 95% power at a 0.05 level to detect a difference of 25% in the percentages of patients achieving weekly average of daily peak Pruritus NRS reduction ≥ 4 at week 16, assuming that the percentages are 36% and 11% for dupilumab Q4W and placebo, respectively.

Efficacy Analysis Sets:

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

The per protocol set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. A major protocol violation is one that may affect the interpretation of study results.

Analysis Methods:

Primary Efficacy Analyses

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

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

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

If a patient withdraws from study, this patient will be counted as a nonresponder

for endpoints after withdrawal.

The Mantel-Fleiss (MF) criterion will be performed, and if it is not met while using the option CMH (MF) in SAS procedure PROC PREQ, sensitivity analyses including each factor separately in CMH test will be conducted. Sensitivity analysis using the last observation carried forward (LOCF) approach to determine patient's status at week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. The efficacy data will be set to missing after rescue treatment is used, then the LOCF method will be used to determine patients' status at week 16.

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

Secondary Efficacy Analyses

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

For continuous endpoints:

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

Multiplicity Consideration

A hierarchical procedure for multiplicity adjustment will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens vs placebo. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level.

Safety Analyses

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACQ	Asthma Control Questionnaire
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ARISg	Pharmacovigilance and clinical safety software system
AST	Aspartate Aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenszel
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CYP	Cytochrome P450
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IAF	Informed assent form
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4R α	IL-4 receptor alpha subunit
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web responses system
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effect model with repeated measures
NAb	Neutralizing antibody
NRS	Numerical Rating Scale
OLE	Open-label extension
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term
QOL	Quality of life
QW	Once a week
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors

TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
TNSS	Total Nasal Symptom Score
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WBC	White blood cell

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 the most common inflammatory skin disease in childhood (Illi 2004). The disease usually presents during early infancy and childhood, but it can persist into or start in adulthood (Kay 1994). The disease affects 15% to 30% of children and 2% to 10% of adults in industrialized countries (Bieber 2008). Phase 1 of the International Study of Asthma and Allergies in Childhood showed a 1-year period prevalence rate as high as 20% in Australia, England, and Scandinavia (Williams 1999). Often, AD constitutes the first step of the “atopic march” (progression from one atopic disease to another). Up to 60% of AD patients have concomitant asthma, allergic rhinitis, or food allergy (Hong 2012).

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 are less likely to have the exudative lesions of infancy, and instead exhibit more lichenified papules and plaques representing the more chronic disease involving the hands, feet, wrists, ankles, and antecubital and popliteal regions. The adult phase of AD begins at puberty and frequently continues into adulthood. 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 patients, greater than that seen in other common skin disorders like psoriasis and acne (Lewis-Jones 1995). 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). In addition to causing discomfort, sleep loss, and psychosocial challenges, AD can impose major financial burdens on families for direct medical care, household accommodations, and missed work (Su 1997, Verboom 2002, Williams 2005).

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

proteins, such as loricrin, filaggrin, involucrin, and the antimicrobial proteins human beta defensin 2 and 3, which in turn, is associated with development of AD ([Howell 2007](#), [Guttman-Yassky 2011a](#), [Guttman-Yassky 2011b](#)). The Th2 cytokines also act on keratinocytes and induce production of chemokines, including chemokine (C-C motif) ligand 17 (also known as thymus and activation-regulated chemokine [TARC]), and chemokine (C-C motif) ligand 26 (also known as eotaxin-3), which are chemo-attractants for Th2 cells and eosinophils; thus, perpetuating the inflammatory response. Since activation of IL-4 and IL-13 signaling precedes the release of proinflammatory mediators, antagonism of these cytokines has the potential to reduce the Th2 response and provide therapeutic benefit.

There is currently a high unmet medical need for a safe and effective therapy for AD in children. Nonpharmacological management of AD, which includes environmental control measures (eg, avoidance of antigen and skin irritants) and skin care measures (eg, maintaining the hydration of the skin through the use of emollients) play a supportive role, especially in children with moderate-to-severe disease. Pharmacological management of AD in children is mainly limited to topical therapy with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). Topical corticosteroids reduce inflammation and pruritus, and are useful in controlling acute flares. 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 many times as an alternative to or in combination with TCS. However, the use of TCI is frequently associated with skin irritation. Furthermore, a possible increased risk of malignancy (lymphoma and skin cancers) has been noted for TCIs (refer to products' US prescribing information).

To date, the only systemic agents approved for the treatment of AD in children are systemic corticosteroids. Other systemic agents are used off label (cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil) and lack robust evidence for the basis of use. All of these systemic agents have significant side effects, 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 ([Granlund 1995](#), [Schmitt 2009](#)).

As a biologic product that selectively targets the Th2 inflammatory pathway, dupilumab is being developed to provide a safe and efficacious alternative treatment for AD patients, including children. Dupilumab is a human monoclonal antibody that targets the IL-4 receptor alpha subunit (IL-4R α), a component of IL-4 receptors Type I and Type II, as well as the IL-13 Type II receptor system. The binding of dupilumab to IL-4R α results in the blockade of both IL-4 and IL-13 signal transduction. Because up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression, dupilumab may be an efficacious alternative AD treatment.

Dupilumab, given subcutaneously (SC), is currently in clinical trials for multiple indications, including treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. As of 30 September 2016, 7408 subjects have been enrolled

into the dupilumab development program (completed and ongoing studies). This includes 222 healthy volunteers, 4182 patients with AD, 2909 patients with asthma, 60 patients with nasal polyps, and 35 patients with eosinophilic esophagitis. In completed or unblinded studies, 3927 subjects have received dupilumab: 202 healthy volunteers, 2853 patients with AD, 842 patients with asthma, and 30 patients with nasal polyps. Taking into account the number of patients exposed to dupilumab in blinded studies, the total number of patients exposed to dupilumab is over 5000. Further, 1 clinical study with dupilumab in the pediatric population has been completed at the time of this protocol development; a phase 2a study (R668-AD-1412) investigating the safety, pharmacokinetics (PK), immunogenicity, and exploratory efficacy of dupilumab in patients aged ≥ 6 to <18 years with AD. A total of 78 pediatric patients were exposed to dupilumab at doses of either 2 mg/kg or 4 mg/kg (single dose, weight dependent), followed by 4 weekly doses of 2 mg/kg or 4 mg/kg (weight-dependent, once a week [QW] regimen). The safety data from this completed study is summarized in section 1.2.3. An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients aged ≥ 6 to <18 years with AD (R668-AD-1434) is currently ongoing.

There is a paucity of clinical studies comparing adults and children, with respect to the cellular and molecular mechanisms of disease in AD. Based on similar clinical presentation and response to treatment, it has been postulated that these mechanisms are similar in adults and children. On this basis, some AD medications (eg, pimecrolimus) were granted regulatory approval in adults even though the pivotal clinical trials were largely conducted in pediatric patients. It is expected that the pharmacological activity of dupilumab will be similar in children and adults.

Nonclinical repeat-dose toxicity studies and reproductive and developmental toxicity studies have shown a lack of any general or reproductive toxicology and postnatal effects observed with anti-IL-4R α 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.

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 on the use of dupilumab monotherapy to support registration and labeling for the use of dupilumab in adolescents with moderate-to-severe AD.

The 16-week treatment duration is the same duration as in 2 of the adult pivotal trials (R668-AD-1416 and R668-AD-1334). This duration has been chosen because the maximum therapeutic effect for dupilumab is expected to be achieved by this time. Moreover, the selected dupilumab dose regimens will have achieved steady-state concentration before the end of this period. Based on PK simulations, in the absence of a loading dose, the time to steady-state is expected to be 12 weeks for 300 mg every 2 weeks (Q2W), and 4 weeks for 300 mg every 4 weeks (Q4W). The use of a loading dose in this study will reduce the time to steady-state for the Q2W regimen, as has been observed in adults, enabling steady-state to be essentially

achieved after 3 doses. The 12 week follow-up period is based on the expected PK of dupilumab after the last dose, ie, the time for serum concentrations to decline to nondetectable levels (below the lower limit of quantification) in most patients.

The co-primary endpoints chosen in the study (proportion of patients achieving Investigator's Global Assessment [IGA] 0 or 1 and proportion of patients with $\geq 75\%$ reduction in Eczema Area and Severity Index [EASI] from baseline [EASI-75] at week 16) are similar to those used in the adult pivotal studies (R668-AD-1334 and R668-AD-1416). These endpoints are both investigator-assessed outcome measures of objective AD signs, which are broadly validated in drug development for this indication. Based on prior discussions with health authorities for the pivotal adult AD studies (R668-AD-1334 and R668-AD-1416), it is expected that different health authorities will request different primary endpoints for this study (Food and Drug Administration [FDA] is expected to request IGA 0/1 as the primary endpoint while EMA is expected to request both EASI-75 and IGA 0/1 as co-primary endpoints). Eczema Area and Severity Index has been validated in the pediatric population, including in patients aged 12 to 17 years old in a prior study ([Barbier 2004](#)).

1.2.2. Rationale for Dose Selection

The dose justification for adolescent pediatric patients aged ≥ 12 to < 18 years is based on the observed efficacy and safety in the dose ranging study in adult AD patients (R668-AD-1021), the observed efficacy and safety in the phase 3 monotherapy studies in adult AD patients (R668-AD-1334 and R668-AD-1416), the observed PK data, efficacy, and safety results in a pediatric AD study of patients ≥ 6 to < 18 years old (R668-AD-1412), and the modeling performed on the PK data obtained from this pediatric study.

The adult dose-ranging study evaluated dupilumab dose regimens of 300 mg QW, 300 mg Q2W, 300 mg Q4W, 200 mg Q2W, and 100 mg Q4W versus placebo, administered for 16 weeks. All 5 dose regimens were efficacious. Efficacy data suggested a dose-response pattern for most efficacy outcome measures, including EASI, IGA, and pruritus scores, for which the corresponding endpoints at week 16 were generally aligned in the same rank order as the total monthly dose and the mean concentrations of functional dupilumab at week 16. Thus, the 300 mg QW regimen was consistently the most efficacious dose regimen in this study across multiple endpoints, followed closely by the 300 mg Q2W dose regimen. Differences in the efficacy and safety outcomes between the 300 mg QW and 300 mg Q2W were relatively small. The 200 mg Q2W and 300 mg Q4W doses also showed good efficacy responses but were numerically inferior to the 300 mg Q2W and 300 mg QW regimens for the majority of efficacy endpoints. The efficacy of the 100 mg Q4W regimen (100 mg total monthly dose) appeared to be sub-optimal.

The dose regimens of 300 mg QW and 300 mg Q2W provided the most consistent clinical benefit and both had an acceptable safety profile. However, 300 mg QW and 300 mg Q2W dosing did not show clear differentiation in EASI and IGA changes from baseline in study R668-AD-1021. More recently, the lack of clear differentiation between 300 mg QW and 300 mg Q2W dosing was further confirmed in 2 pivotal studies (R668-AD-1334 and R668-AD-1416) in adults based on EASI and IGA data. As PK modeling for dupilumab has shown weight to be the most important covariate influencing exposure, the use of the 300 mg QW regimen in adolescents with low body weight may lead to systemic exposure greater than

the maximum exposure that has been tested in adults. Therefore, 300 mg QW is not considered appropriate for adolescents. With the 300 mg Q2W regimen in adolescents ≥ 60 kg, the simulated exposure in adolescents substantially overlaps with the range of exposure in individual patients in studies R668-AD-1021 (300 mg Q2W and 300 mg QW) and DRI12544 (300 mg Q2W), where no significant safety risk was identified. Hence, the proposed 300 mg Q2W dosing regimen for adolescent patients weighing ≥ 60 kg is expected to have a significant clinical benefit with an appropriate safety profile. A similar exposure response to dupilumab treatment is anticipated between adolescent and adult AD patients, supporting dose selection by matching PK exposure with adults, for a clinical efficacy study in adolescent patients.

Data from R668-AD-1021 also showed that a dose regimen of 200 mg Q2W was significantly superior to placebo on key efficacy endpoints. The use of 200 mg Q2W is expected to provide mean exposure in adolescents < 60 kg similar to that with 300 mg Q2W in adolescents ≥ 60 kg supporting the use of this regimen in the lower weight cohort. Moreover, the 200 mg dose can be delivered using a 1 mL volume of injection. Since volume of injection has been shown to be an important factor impacting the tolerability of SC injections (Heise 2014), a 200 mg injection is expected to be less painful than a 300 mg injection. This might impact compliance and ultimately the therapeutic profile of the drug, especially in a pediatric population. Also, a 1 mL autoinjector device has already been commercialized for other monoclonal antibodies.

Study R668-AD-1021 demonstrated that efficacy for the 300 mg Q4W regimen was statistically superior to placebo and numerically similar to the 300 mg Q2W and 200 mg Q2W dose regimens. Pharmacokinetic simulation has shown that although this dose regimen is expected to provide lower exposure to the other 2 dupilumab dose regimens being studied, it should still have sufficient exposure to provide significant clinical benefit in adolescents. Data gathered from this dose regimen will also enable further PK modeling to better characterize exposure response relationship in pediatric patients. A less frequent dosing regimen is expected to enhance compliance, especially in a pediatric population.

In study R668-AD-1412, weekly doses of up to 4 mg/kg SC were shown to be generally well tolerated in pediatric patients aged 6 to 17 years old. The exposure for all proposed doses in the current study is expected to be lower in most patients than what was seen with use of repeated weekly doses of 4 mg/kg in the previous study.

An advantage of fixed weight-based dosing compared to variable weight-based dosing is to allow self-administration using a prefilled syringe.

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

1.2.3. Safety Considerations

The safety profile of dupilumab is not expected to be different between adults and adolescents. Data gathered from the completed R668-AD-1412 study support this view.

R668-AD-1412 was a phase 2a study to evaluate the PK and safety of dupilumab in patients aged ≥ 6 years to < 18 years, with moderate-to-severe AD. Dupilumab administered as single and repeated weekly doses of 2 mg/kg and 4 mg/kg for 4 weeks was generally well tolerated in both pediatric age groups included in this study. There was a higher incidence of treatment-emergent

adverse events (TEAEs) after administration of the single dose 4 mg/kg dupilumab in both age-groups. Similarly, there was a higher incidence of TEAEs after administration of repeated weekly doses of 4 mg/kg in both age-groups. However, most of the AEs were mild in intensity, transient in nature, and not related to study drug. There were no new safety signals detected with dupilumab in this pediatric population. The most common AEs reported after both single doses and repeated weekly doses were Nasopharyngitis and Exacerbation of AD.

Standard safety monitoring used in previous trials with dupilumab is planned to be conducted during this study. An IDMC overseeing the entire dupilumab clinical development will be in place for the duration of the study to monitor the safety of the patients and to provide the sponsor with appropriate recommendations in due time to ensure the safety of the patients.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab as a monotherapy in patients ≥ 12 years to < 18 years of age with moderate-to-severe AD.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety of dupilumab as a monotherapy in patients ≥ 12 years to < 18 years of age with moderate-to-severe AD.

3. STUDY DESIGN

3.1. Study Description and Duration

This is a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of dupilumab monotherapy in pediatric patients with moderate-to-severe AD. The study population will include patients ≥ 12 years to < 18 years of age with 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). Approximately 240 study patients are planned to be randomized to 1 of the following treatment groups:

- Dupilumab Q2W treatment group: 200 mg Q2W for patients < 60 kg or 300 mg Q2W for patients ≥ 60 kg
- Dupilumab Q4W treatment group: 300 mg Q4W, irrespective of weight
- Placebo group

The study will consist of the following 3 periods: screening of up to 5 weeks, treatment period of 16 weeks, and follow-up of 12 weeks ([Figure 1](#)).

After the parents or legal guardians/patients provide informed consent and informed assent (as appropriate), the patients will be assessed for study eligibility at the screening visit. During the screening period, systemic and topical treatments for AD will be washed out, as applicable,

according to the eligibility requirements. Patients may be rescreened once 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 and continue throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of nonlesional skin designated for such assessments for at least 8 hours before each clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio stratified by baseline weight group (<60 kg and ≥60kg; each weight stratum will enroll approximately 120 patients) and baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) as follows:

- Dupilumab Q2W treatment group: Patients with baseline weight <60 kg will receive Q2W SC injections of 200 mg dupilumab following a loading dose of 400 mg on day 1. Patients with baseline weight ≥60 kg will receive Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Dupilumab Q4W treatment group: Patients will receive Q4W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Placebo treatment group: Patients will receive placebo matching dupilumab Q2W (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, patients in the <60 kg weight stratum will receive, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the patients randomized to the placebo group will receive placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

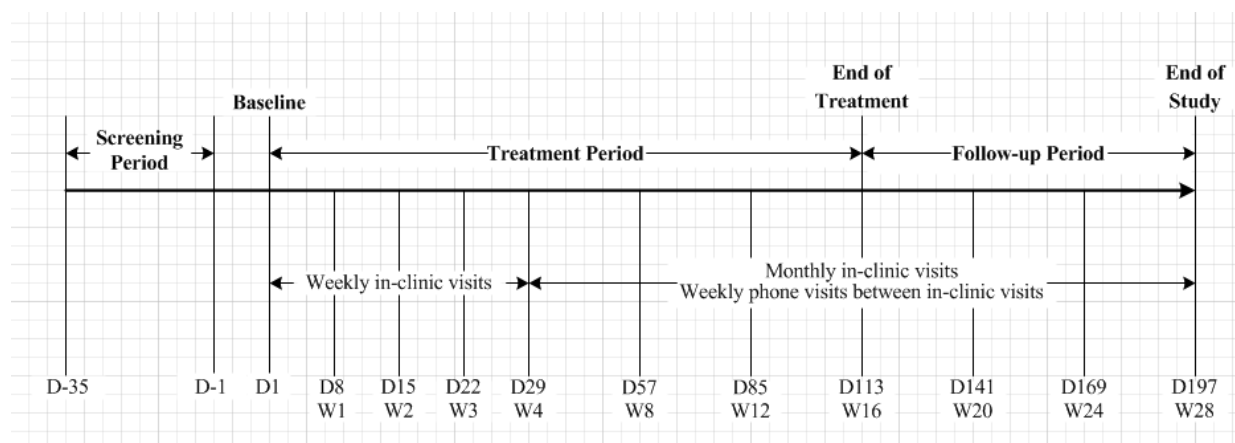
In order to maintain blinding, all patients will receive an injection Q2W from day 1 to week 14. Patients will receive placebo injection at the weeks dupilumab is not given.

During the treatment period, patients will have weekly in-clinic visits through week 4, and then in-clinic visits every 4 weeks through week 16 with weekly telephone visits in between the in-clinic visits. Patients and/or parents/caregivers (as deemed appropriate based on age of patient) will be trained on injecting study drug during in-clinic visit 2 (day 1) to visit 6 (week 4). During weeks in which no in-clinic visit is scheduled, patients will either self-inject study drug or the parent/caregiver will administer study drug to the patient. In case patients do not want to self-inject and the parent/caregiver do not want to administer study drug to patient, patients may have the clinic staff administer all the study drug injections in the clinic. Safety, laboratory, and clinical assessments will be performed at specified clinic visits, as noted in [Table 1](#). The end of treatment period visit will occur at week 16, two weeks after the last dose of study drug. The co-primary endpoints will be assessed at this visit. If patients prematurely discontinue study treatment, the patients will be encouraged to stay in the study to have data collected at all remaining scheduled visits until completion of the planned end of study visit.

Patients who participate in the study may subsequently be eligible to participate in an open-label extension study.

Patients who decline to enroll in the open-label extension study will be followed up for 12 weeks. For these patients, after week 16, 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 per schedule as noted in [Table 2](#).

Figure 1: Study Flow Diagram



D = study day; W = study week

3.1.1. End of Study Definition

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

3.2. Planned Interim Analysis

No interim analysis with alpha spending is planned for this study. An unblinded first-step analysis **may** be performed once all patients in the study have completed the 16-week treatment period, as specified in the protocol (week 16 visit or earlier for those patients who are withdrawn prematurely from the study). If performed, this first-step analysis will be considered the final analysis for the primary and secondary efficacy endpoints. A description of the statistical methods to be employed and blinding implications are in section [9.5.2.4](#).

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 by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC

will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

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

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Approximately 240 patients are planned to be enrolled into 3 groups (80 per group): dupilumab Q2W treatment groups (200 mg Q2W or 300 mg Q2W), dupilumab Q4W treatment group (300 mg Q4W), or placebo group. The study will be conducted at multiple sites in North America; other regions may be included.

4.2. Study Population

The study population includes pediatric patients (aged ≥ 12 to < 18 years at the time of baseline) who have moderate-to-severe AD that cannot be adequately controlled with topical AD medications or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects or safety risks).

4.2.1. Inclusion Criteria

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

1. Male or female ≥ 12 to < 18 years of age at time of screening visit
2. Diagnosis of AD according to the American Academy of Dermatology consensus criteria ([Eichenfield 2014](#)) at screening visit
3. Chronic AD diagnosed at least 1 year prior to the screening visit
4. IGA ≥ 3 at screening and baseline visits
5. EASI ≥ 16 at the screening and baseline visits
6. Baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥ 4

NOTE: Baseline Pruritus NRS average score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. 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 35-day maximum duration for screening.

7. $\geq 10\%$ body surface area (BSA) of AD involvement at the screening and baseline visits

8. With documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s) or for whom topical treatments is medically inadvisable (eg, intolerance, because of important side effects or safety risks). For more information, see the note below.

NOTE:

- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency ($\pm$ TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever is shorter.
 - Patients with documented systemic treatment (systemic immunosuppressant drugs like cyclosporine, methotrexate, corticosteroids etc.) 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.
 - Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the patient's treating physician.
 - 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 or higher potency ($\pm$ 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 during this period, as defined above, will be eligible for inclusion in the study following appropriate washout.
9. Has applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (see exclusion criterion 9 regarding restrictions on the kind of emollients permitted during the study)
10. Willing and able to comply with all clinic visits and study-related procedures
11. Able to understand and complete study-related questionnaires
12. Parent or legal guardian must provide signed informed consent. Patients must also provide separate informed assent to enroll in the study, and sign and date either a separate informed assent form (IAF) or the informed consent form (ICF) signed by the parent/legal guardian (as appropriate based on local regulations and requirements)

4.2.2. Exclusion Criteria

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

1. Participation in a prior dupilumab clinical study
2. Treatment with a systemic investigational drug before the baseline visit
3. Treatment with a topical investigational agent within 4 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
4. Treatment with TCS or TCI within 2 weeks before the baseline visit (patients may be rescreened)
5. Having used any of the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment:
 - a. Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
 - b. Phototherapy for AD
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 before the baseline visit, whichever is longer
7. Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit

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

 - Patients for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
 - Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.
8. Planned or anticipated use of any prohibited medications and procedures during study treatment
9. Treatment with crisaborole within 2 weeks prior to the baseline visit.
10. Body weight <30 kg at baseline

11. 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)
12. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit
13. 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

14. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune-compromised status, as judged by the investigator
15. Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit
16. With an established diagnosis of hepatitis B viral infection at the time of screening or is positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) at the time of screening

NOTE: Patients who have gained immunity for hepatitis B virus infection after vaccination (patients who are HBsAg negative, hepatitis B surface antibody [HBsAb] positive, and HBcAb negative) are eligible for the study. These patients will be allowed to enroll into the study, but will be followed using routine clinical and liver function tests.

17. With an established diagnosis of hepatitis C viral infection at the time of screening or is positive for hepatitis C antibody at the screening visit
18. 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 1 or more of the following abnormalities in laboratory test results at screening:
 - Platelets $\leq 100 \times 10^3/\mu\text{L}$
 - Neutrophils $< 1.5 \times 10^3/\mu\text{L}$
 - Creatine phosphokinase (CPK) $> 5 \times \text{ULN}$
 - Serum creatinine $> 1.5 \times \text{ULN}$

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

20. Presence of skin comorbidities that may interfere with study assessments
21. History of malignancy 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. History of alcohol or drug abuse within 2 years before the screening visit, or evidence of such abuse as documented by a positive result in a laboratory test for alcohol and/or drug panel conducted at the screening visit

Note: If a patient has a positive drug test for a prescription drug being used for medical reasons, the patient would still be eligible for enrollment. In such cases, the site would need to confirm the medical reason for use with the treating physician.

24. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to patients with short life expectancy, patients with uncontrolled diabetes (hemoglobin A1c $\geq 9\%$), patients with cardiovascular conditions (eg, Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRF], etc).
25. 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).
26. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities will be excluded from this study.
27. Planned major surgical procedure during the patient's participation in this study
28. Patient or his/her immediate family is a member of the dupilumab investigational team
29. Patient is female who is pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study

30. Patient is female of childbearing potential* and sexually active, who is unwilling to use adequate methods of contraception** throughout the duration of the study and for 120 days after the last dose of study drug

- * For the purpose of this study, any female who has had her first menstrual period (menarche) and is sexually active will be considered to be of childbearing potential. Female patients who are not of childbearing potential at the start of the study but have the onset of menarche during the course of the study and are sexually active will also have to follow adequate birth control methods to continue participation in the study.
- ** Adequate methods of contraception include: female sterilization (with documented hysterectomy, bilateral oophorectomy or bilateral tubal ligation), hormonal contraceptives, intrauterine device, or condom + diaphragm***, or single male partner with documented vasectomy. Additional requirements for acceptable contraception may apply in certain countries, based on local regulations. Investigators in these countries will be notified accordingly in a Protocol Clarification Letter***.
- *** The study may enroll patients from sites in the UK. Double barrier methods (eg, condom + diaphragm) would not be considered adequate methods of contraception for patients enrolled in the UK for the purpose of this study.

4.3. Premature Withdrawal from the Study

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

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

Patients who withdraw prematurely from the study will be asked to complete study assessments per section 6.1.

4.4. Replacement of Patients

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

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

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

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

Placebo matching dupilumab is prepared in the same formulation without the addition of protein (ie, active substance, anti-IL-4R α monoclonal antibody).

Patients will be randomized to receive 1 of the following treatment regimens:

- Dupilumab Q2W treatment:
 - Patients <60 kg in baseline body weight: SC injections of dupilumab, 400 mg loading dose on day 1, then 200 mg Q2W from week 2 to week 14, or
 - Patients $\geq$ 60 kg in baseline body weight: SC injections of dupilumab, 600 mg loading dose on day 1, then 300 mg Q2W from week 2 to week 14
- Dupilumab Q4W treatment: SC injections of dupilumab, 600 mg loading dose on day 1, then 300 mg Q4W from week 4 to week 12; in order to maintain the blind, there will be an SC injection of placebo in between dupilumab doses during the week 2 to week 14 dosing period so the injection frequency will match the other 2 groups.
- Placebo: SC injections of placebo matching dupilumab Q2W (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, patients in the <60 kg weight stratum who are randomized to the placebo group will receive, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the $\geq$ 60 kg weight stratum, the patients randomized to the placebo group will receive placebo matching 300 mg dupilumab.

In order to maintain blinding, all patients will receive an injection Q2W from day 1 to week 14. Patients will receive placebo injection at the weeks dupilumab is not given.

Study drug will be administered per the scheduled described in section 6.1.

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

Patients will have the option to administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no in-clinic visit is scheduled. The study staff will train the patient/caregiver on preparation and administration of study drug on day 1 and will administer the first of the 2 injections required for the loading dose. The patient/caregiver will administer the second injection required for the loading dose under the supervision of the clinic staff. The patient/caregiver will administer study drug under the supervision of the clinic staff at visits 4 and 6 (weeks 2 and 4, respectively) and at other in-clinic visits. Patients will be monitored at the study site for a minimum of 30 minutes after the first 3 doses of study drug (visits 2 [day 1], 4 [week 2], and 6 [week 4]); vital signs (sitting blood pressure, heart rate, and respiratory rate) and AE assessments will be done at 30 minutes ($\pm$ 10 minutes) post dose. The

patient (or caregiver) will administer study drug outside of the clinic during weeks in which no clinic visit is scheduled.

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

5.2. Background Treatment

All patients are required to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization. After randomization, patients are required to continue to apply moisturizers throughout the study (all 28 weeks where applicable).

However, to allow adequate assessment of skin dryness, moisturizers should not be applied for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers 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.

5.3. Rescue Treatment

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. If possible, investigators are encouraged to consider rescue initially with topical treatment (eg, medium/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 nonsteroidal immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc) as rescue medication during the study will be discontinued permanently from the study drug. All patients will be asked to complete the scheduled study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety laboratory tests) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary. For the purpose of efficacy analysis, patients who receive rescue treatment during the study will be considered treatment failures.

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

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

Patients who opt to withdraw from the study will be asked to complete study assessments, per section 6.1.

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 study drug
- Repeated (2 or more during the course of the study) severe injection site reactions that are deemed to be immune mediated*

* This is based on investigator's assessment. A consultation with the medical monitor can be sought to determine the exact etiology of an injection site reaction.

- Diagnosis of a malignancy during study
- Evidence of pregnancy
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities:
 - Neutrophil count $\leq 0.5 \times 10^3/\mu\text{L}$
 - Platelet count $\leq 50 \times 10^3/\mu\text{L}$
 - ALT and/or AST values greater than $3 \times \text{ULN}$ with total bilirubin $> 2 \times \text{ULN}$ (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
 - Confirmed AST and/or ALT $> 5 \times \text{ULN}$ (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 TCS, TCI and crisaborole is prohibited during the study. However, these drugs may be used as rescue. In that case, the study drug will be continued.

5.4.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
 - ALT or AST $3 \times$ ULN
 - Neutrophil count $<1.5 \times 10^3/\mu\text{L}$ but $>0.5 \times 10^3/\mu\text{L}$
 - Platelet count $\leq 100 \times 10^3/\mu\text{L}$ but $>50 \times 10^3/\mu\text{L}$
 - CPK $>5 \times$ ULN
 - Serum creatinine $>1.5 \times$ ULN
- Other intercurrent illnesses or major surgery
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents, or requires oral treatment with such agents for longer than 2 weeks

After the condition leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. A decision to discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. 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

Approximately 240 patients will be randomized by weight group (<60 kg or ≥ 60 kg [with approximately 120 patients to each weight group]) and by baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) to 1 of the following treatment groups according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee):

- Dupilumab Q2W treatment groups: Patients whose baseline weight <60 kg will receive Q2W SC injections of 200 mg dupilumab following a loading dose of 400 mg on day 1. Patients whose baseline weight ≥ 60 kg will receive Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Dupilumab Q4W treatment group: Patients will receive Q4W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.
- Placebo treatment group: Patients will receive placebo matching dupilumab Q2W (including doubling the amount of placebo on day 1 to match the loading dose). In the <60 kg weight stratum, since the dose level (ie, 300 mg or 200 mg) won't be blinded, in order to maintain blinding for the study, the patients in the <60 kg weight stratum who are randomized to the placebo group will receive, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including

doubling the amount of placebo on day 1 to match the loading dose). In the ≥ 60 kg weight stratum, the patients randomized to the placebo group will receive placebo matching 300 mg dupilumab.

5.5.1. Blinding

With the exception of the IDMC members and the provisions in section 5.5.2, this study will remain blinded to all individuals until the prespecified unblinding to conduct the primary analyses.

Blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct. To maintain the blind, all patients will receive Q2W injections of dupilumab or placebo starting at day 1. During weeks in which dupilumab is not administered in the Q4W dosing regimen, patients will receive placebo.

Anti-drug antibody (ADA) 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

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

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

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

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

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

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped [REDACTED] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study

(eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

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

All drug compliance records 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 final 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 study manual for a current, comprehensive list of prohibited vaccines

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

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating biologics
- Treatment with systemic nonsteroid immunosuppressant (may be used as rescue, see section 5.3 for details)
- Treatment with systemic corticosteroids (may be used as rescue, see section 5.3 for details)
 - Treatment with TCS or TCI (may be used as rescue, see section 5.3 for details)
- Treatment with crisaborole (may be used as rescue, see section 5.3 for details)
- Initiation of treatment of AD with prescription moisturizers

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Tanning in a bed/booth
 - Phototherapy (UVA, UVB, nbUVB, high dose UVA and PUVA)

5.7.2. Permitted Medications and Procedures

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

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

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

Patients who complete the treatment period (week 16) will be offered an opportunity to screen for the open-label extension (OLE) at end of treatment visit. These patients should complete the end-of-treatment [EOT] visit (as per Table 2) before screening for the OLE. Patients who discontinued prematurely (ie patients who did not complete the protocol-defined end-of-treatment [EOT] visit) cannot screen for the OLE study before the date when the EOT visit (week 16) would have normally occurred. Patients who decline to participate in the OLE study will have a 12-week follow-up period.

NOTE: Patients who turned 18 years of age during this study will not be eligible to enroll into the pediatric open-label extension study (R668-AD-1434). In case the drug is not commercially available for patients aged ≥ 18 years at the time the patient completes this study, these patients may be eligible for, and might have the opportunity to, enroll into the adult open-label extension study (R668-AD-1225), if the study is still ongoing.

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](#) (Screening, Baseline, and Treatment Period) and in [Table 2](#) (Treatment Period cont, Follow-up Period, Unscheduled Visits, and Early Termination).

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

	Screening	Treatment Period												
		BL												
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	PV7 ^a	PV8 ^a	PV9 ^a	V10	PV11 ^a	PV12 ^a	PV13 ^a	V14
Week (W)			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Study Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Window in days			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Screening/Baseline:														
Informed consent/assent	X													
	X													
Medical history	X													
Demographics	X													
Inclusion/exclusion criteria	X	X												
Randomization		X												
Patient ed diary training for pruritus assessments, TNSS assessment, and emollient use ^c	X	X												
Treatment:^d														
Injection training/observation ^e		X		X		X				X				X
Study drug administration		X ^f		X ^f		X ^f		X		X		X		X
Patient/parent(s) or caregiver paper diary training for dosing						X								
Patient dosing diary completion								X				X		
Study drug dispensation ^g						X				X				X
Study drug accountability ^g										X				X
Review home ed diary		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Treatment Period												
		BL												
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	PV7 ^a	PV8 ^a	PV9 ^a	V10	PV11 ^a	PV12 ^a	PV13 ^a	V14
Week (W)			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Study Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Window in days			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Efficacy: ^d														
Patient assessment of pruritus intensity using NRS via diary (daily) ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient assessment of pruritus intensity using PCS via diary (daily) ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment of disease ^h	X	X		X		X				X				X
Patient global assessment of treatment ^h				X		X				X				X
^h Patient-reported CDLQI ⁱ , POEM ⁱ , HADS ⁱ	X	X		X		X				X				X
^h Patient-reported ACQ-5 ^{i,j}	X	X												
Patient-reported TNSS ^{h,i,k}		X				X								
Patient assessment of injection pain using VAS ^h		X		X		X				X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X	X	X				X				X
Assess missed school days		X				X				X				X
Photograph AD areas (select sites)		X												
Safety: ^d														
Weight	X	X												
Height	X													
Vital signs	X	X ^f	X	X ^f	X	X ^f				X				X
Physical examination	X													
ECG	X													
Adverse events	X	X ^f	X	X ^f	X	X ^f	X	X	X	X	X	X	X	X

	Screening	Treatment Period												
		BL												
In-clinic Visit (V) or Phone Visit (PV)	V1	V2	V3	V4	V5	V6	PV7 ^a	PV8 ^a	PV9 ^a	V10	PV11 ^a	PV12 ^a	PV13 ^a	V14
Week (W)			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Study Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Window in days			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Laboratory Testing: ^d														
Hematology	X	X				X				X				
Chemistry ^m	X	X				X				X				
Urinalysis ^m	X	X				X								
Alcohol & drug screen test	X													
Pregnancy test, WOCBP only	Serum	Ur	Ur	Ur	Ur	Ur				Ur				Ur
HIV, HBsAg, HBsAb, HBcAb, Hep C Ab, TB ^l	X													
Biomarker: ^d														
TARC	X	X		X		X				X				X
Total serum IgE, immunoglobulin profiling, antigen specific IgE	X	X				X				X				X
Biomarker samples (serum)		X				X				X				
		X												
Drug Concentration and ADA: ^d														
Functional dupilumab concentration sample		X		X		X				X				X
ADA sample		X				X								

BL = baseline; Ur = urine; WOCBP = women of childbearing potential; TB = tuberculosis

^a The site will contact the patient/caregiver by telephone to conduct these visits. The patient/caregiver may administer study drug during phone visits. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and to document any related issues.

- ^c Training of patients regarding completion of diary to record (1) completion of assessment of Pruritus NRS scale, (2) completion of assessment of Pruritus Categorical Scale, (3) completion of assessment of Total Nasal Symptoms Score (TNSS), and (4) emollient usage.
- ^d Assessments/procedures should be conducted in the following order: patient reported outcomes (other than patient assessment of injection pain), investigator assessments, safety and laboratory assessments (including sample collection for ADA, PK, biomarker, and optional DNA and RNA), and administration of study drug.
- ^e Patients or parents/caregivers will be trained on how to administer study drug. This will enable administration at home in between clinic visits.
- ^f Patients will be monitored at the study site at visits 2, 4, and 6 for a minimum of 30 minutes after study drug administration. Vital signs (sitting blood pressure, heart rate, and respiratory rate) and AEs will be assessed at 30 minutes (± 10 minutes) post-injection.
- ^g Starting at visit 6, study drug will be dispensed to the patients or parents/caregivers for the dose that will be administered before the next clinic visit. Patients or parents/caregivers will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. At these in-clinic visits, sites will perform accountability assessment for the study drug that the patients or parents/caregivers have returned to the site.
- ^h Patient-reported assessments are to be completed only by the patient.
- ⁱ The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).
- ^j ACQ-5 will be administered only to patients with ongoing asthma.
- ^k TNSS will be administered only to patients with medical history of allergic rhinitis throughout the screening period (at least 7 days before baseline/day 1) and only for 7 days preceding visit 6.
- ^l Tuberculosis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.
- ^m If baseline/day 1 visit occurs within 14 days of screening, hematology and serum chemistry do not need to be repeated at the baseline/day 1 visit as long as these assessments were performed at the screening visit.

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

Study Procedure	Treatment Period				Follow-Up Period ⁱ			Unscheduled Visit ^b	Early Termination Visit
				EOT ⁱ			EOS		
In-clinic Visit (V)	PV15 ^a	PV16 ^a	PV17 ^a	V18	V19	V20	V21		
Week (W)	W13	W14	W15	W16	W20	W24	W28		
Study Day (D)	D92	D99	D106	D113	D141	D169	D197		
Window in days	±3	±3	±3	±3	±4	±4	±4		
Treatment:^c									
Study drug administration		X							
Patient dosing paper diary completion		X							
Study drug accountability ^d				X				X	X
Review home ed diary	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X
Efficacy:^c									
Patient assessment of pruritus intensity using NRS via diary (daily) ^e	X	X	X	X	X	X	X	X	X
Patient assessment of pruritus intensity using PCS via diary (daily) ^e	X	X	X	X	X	X	X	X	X
Patient global assessment of disease ^e				X	X	X	X	X	X
Patient global assessment of treatment ^e				X	X	X	X	X	X
^e Patient-reported CDLQI ^f , POEM ^f , HADS ^f				X	X	X	X	X	X
^e Patient-reported ACQ-5 ^g				X			X		X
Patient-reported TNSS ^{e, f, h}				X			X		
Patient assessment of injection pain using VAS ^h									
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
Assess missed school days				X	X	X	X	X	X
Photograph AD areas (select sites)				X			X		X
Safety:^c									
Weight				X			X		X
Height				X			X		X
Vital signs				X	X	X	X	X	X
Physical examination				X			X	X	X
ECG				X			X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Study Procedure	Treatment Period				Follow-Up Period ⁱ			Unscheduled Visit ^b	Early Termination Visit
				EOT ¹			EOS		
In-clinic Visit (V)	PV15 ^a	PV16 ^a	PV17 ^a	V18	V19	V20	V21		
Week (W)	W13	W14	W15	W16	W20	W24	W28		
Study Day (D)	D92	D99	D106	D113	D141	D169	D197		
Window in days	±3	±3	±3	±3	±4	±4	±4		
Laboratory Testing:^c									
Hematology				X			X	X	X
Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy test, WOCBP only				Urine			Urine	Urine	Urine
Biomarker:^c									
TARC				X			X	X	X
Total Serum IgE, immunoglobulin profiling, antigen specific IgE				X			X	X	X
Biomarker samples (serum)				X					
Drug Concentration and ADA Samples:^c									
Functional dupilumab concentration sample				X			X	X	X
ADA sample				X			X	X	X

EOT = End of Treatment; EOS = End of Study

^a The site will contact the patient/caregiver by telephone to conduct these visits. The patient/caregiver may administer study drug during phone visits. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and to document any related issues.

^b Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason (eg, before a rescue medication/procedure is used), as warranted.

^c Assessments/procedures should be conducted in the following order: patient reported outcomes (other than patient assessment of injection pain), investigator assessments, and safety and laboratory assessments (including sample collection for ADA, PK, and biomarkers). Samples positive in the ADA assay will be analyzed in the neutralizing antibody (NAb) assay.

^d Patients or parents/caregivers will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. At these in-clinic visits, sites will perform accountability assessment for the study drug that the patients or parents/caregivers have returned to the site.

^e Patient-reported assessments are to be completed only by the patient.

^f The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).

^g ACQ-5 will be administered only to patients with ongoing asthma.

^h Total Nasal Symptoms Score will be administered only to patients with medical history of allergic rhinitis for 7 days preceding visit 18 and visit 21.

ⁱ The follow-up period will be for those patients who decline to enter the open-label extension study.

6.2. Study Procedures

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

1. Patient Reported Outcomes (other than patient assessment of injection pain)
2. Investigator assessments (performed only by adequately trained and qualified investigators or sub-investigators; it is recommended that the same investigator or sub-investigator perform all the evaluations for a given patient throughout the entire study period)
3. Safety and laboratory assessments (including sample collection for ADA, PK, biomarker, and optional DNA and RNA).
4. Administration of study drug

6.2.1. Procedures Performed only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: medical history and demographics.

6.2.2. Efficacy Procedures

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

Questionnaires and patient-reported assessments should be administered prior to obtaining investigator assessments, safety and laboratory assessments, and study drug administration. Please see study manual for instructions on the administration and use of all patient-reported instruments (including Pruritus NRS, patient global assessment of disease, patient global assessment of treatment, Children's Dermatology Life Quality Index [CDLQI], Patient Oriented Eczema Measure [POEM], and Hospital Anxiety and Depression Scale [HADS]).

6.2.2.1. Patient Assessment of Pruritus Using Numerical Rating Scale

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a 24-hour recall period. Patients will be asked the following question:

For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"

Patients will be instructed on using the patient diary to record their Pruritus NRS score at the screening and baseline visits. Patients will complete the rating scale DAILY throughout the entire study (screening period, treatment period, and follow-up period; see time point in section 6.1). Clinical sites will check and remind patient to complete the diary at each visit.

6.2.2.2. Patient Assessment of Pruritus Using Pruritus Categorical Scale

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in previous clinical studies of AD, and there is less of a tendency for patients to provide an “average” response than there might be with a 5-point scale (Kaufmann 2006). The scale is rated as follows: 0 = absence of pruritus; 1 = mild pruritus (occasional slight itching/scratching); 2 = moderate pruritus (constant or intermittent itching/scratching that does not disturb sleep); and 3 = severe pruritus (bothersome itching/scratching that disturbs sleep). Patients will be instructed on using the patient diary to record their pruritus categorical scale score at the screening and baseline visits. Patients will complete the rating scale DAILY throughout the entire study (screening period, treatment period, and follow-up period; see time point in section 6.1). Clinical sites will check and remind patient to complete the diary at each visit.

6.2.2.3. Patient Global Assessment of Disease

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

Overall, how would you rate your eczema symptoms right now?

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

Patients will undergo this assessment at time points according to section 6.1.

The assessment tool is provided in the study reference manual.

6.2.2.4. Patient Global Assessment of Treatment

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

Compared to before you started the study, how would you rate your eczema symptoms now?

- Much better
- A little better
- No difference
- A little worse
- Much worse

Patients will undergo this assessment at time points according to section 6.1.

The assessment tool is provided in the study reference manual.

6.2.2.5. Children's Dermatology Life Quality Index

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

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

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

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

Patients will undergo this assessment at time points according to section [6.1](#).

The CDLQI is provided in the study reference manual.

6.2.2.6. Patient Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults ([Charman 2004](#)). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency of these disease symptoms during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity. The questionnaire will be administered at time points according to section [6.1](#).

6.2.2.7. Patient-Assessed Hospital Anxiety and Depression Scale

The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state ([Zigmond 1983](#), [Herrmann 1997](#)). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. The questionnaire will be administered only to the subset of patients who fluently speak a language in which the

questionnaire is presented (based on availability of validated translations in participating countries), at time points according to section 6.1.

The HADS is provided in the study reference manual.

6.2.2.8. Juniper Asthma Control Questionnaire – 5

The 5-question version of the Juniper Asthma Control Questionnaire (ACQ) is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with ongoing asthma and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at time points according to section 6.1.

The assessment tool is provided in the study reference manual.

6.2.2.9. Total Nasal Symptom Score

The Total Nasal Symptom Score (TNSS) will be used to assess the effect of study drug on symptoms of allergic rhinitis. The summed score will include the following 5 symptoms: rhinorrhea, nasal congestion, nasal itching, sneezing, and difficulty in sleeping, each rated on a 0 to 3 scale of severity. This instrument has been extensively used in previous trials conducted in patients with allergic rhinitis (Berger 2015, Benninger 2010). The questionnaire will be administered only to the subset of patients with a medical history of allergic rhinitis who fluently speak a language in which the questionnaire is presented (based on availability of translations in participating countries). Patients will be instructed on using the patient diary to record their TNSS throughout the screening period (at least 7 days before baseline/day 1) and only for 7 days preceding visit 6, visit 18, and visit 21.

The assessment tool is provided in the study reference manual.

6.2.2.10. Injection Site Pain Visual Analogue Scale

Patients will be asked to provide an assessment of pain experienced during injection of study drug using a Visual Analogue Scale (VAS). This assessment will be performed after injection of the study drug at certain in-clinic visits according to section 6.1.

The assessment tool is provided in the study reference manual.

6.2.2.11. Investigator's Global Assessment

The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score will be assessed at time points according to section 6.1.

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

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 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.

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

6.2.2.13. Global Individual Signs Score

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria (section 6.2.2.12). The Global Individual Signs Score (GISS) will be assessed at time points according to section 6.1.

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

6.2.2.14. SCORing Atopic Dermatitis

The SCORing Atopic Dermatitis (SCORAD) is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (European Task Force on Atopic Dermatitis 1993). There are 3 components to the assessment: A = extent or affected BSA, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see section 6.2.2.15) and reported as the sum of all areas, with a maximum score of 100% (assigned as “A” in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, and dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as “B” in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a Visual Analogue Scale, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as “C” in the overall SCORAD calculation. The SCORAD is calculated as: $A/5 + 7B/2 + C$ where the maximum is 103. Patients will undergo this assessment at time points according to section 6.1.

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

6.2.2.15. Body Surface Area Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body using the rule of nines (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. Patients will undergo this assessment at time points according to section 6.1.

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

6.2.2.16. Assessment of Missed School Days

Patients who are enrolled in school will be asked to report the number of missed school days since the last study assessment. Patients will undergo this assessment at time points according to section 6.1.

The assessment tool is provided in the study reference manual.

6.2.2.17. Atopic Dermatitis Area Photographs

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

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

6.2.3. Safety Procedures**6.2.3.1. Vital Signs**

Vital signs (including sitting blood pressure, heart rate, respiration, and temperature) will be collected at predose at every in-clinic visit. At the first 3 administrations of study drug (day 1, week 2 and week 4), sitting blood pressure, heart rate, and respiratory rate will also be assessed at 30 ($\pm$ 10) minutes postdose. See section 6.1 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.

6.2.3.3. Physical Examination

A thorough and complete physical examination will be performed at visits according to section 6.1. 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 should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead electrocardiogram (ECG) will be performed at time points according to section 6.1. Heart rate will be recorded from the ventricular rate, and the PR, QRS, RR and QT intervals will be recorded. The ECG strips or reports will be retained with the source.

6.2.3.5. Laboratory Testing

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

Samples for laboratory testing will be collected at time points according to section 6.1. Tests will include:

Serum Chemistry

Sodium	Total protein, serum	Total bilirubin ¹
Potassium	Creatinine	Total cholesterol ²
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	AST	Uric acid
Calcium	ALT	CPK ³
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

1 Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN

2 Low-density lipoprotein and high-density lipoprotein

3 CPK isoenzymes will be measured when CPK >5× the ULN

Hematology

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

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Serum and urine pregnancy testing will be performed for all female patients of childbearing potential at time points according to section 6.1. The following tests will be performed at screening: HIV, HBsAg, HBsAb, HBeAb, hepatitis C antibody, tuberculosis (will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards), and alcohol and drug screen test.

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](#).

6.2.4. 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](#).

6.2.4.2. Anti-Drug Antibody Measurements and Samples

Serum samples for ADA assessment will be collected at time points listed in section [6.1](#).

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

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

Patients with total serum IgE levels in the normal range may still have antigen-specific IgE in circulation, indicating they are atopic. To further understand atopy in this patient population, region-specific, allergen-specific IgE panels will be performed. These markers may be used to understand PD activity, efficacy, and may be also tested for predictive utility.

Serum samples for measurements of biomarkers (including TARC, total IgE, immunoglobulin profiling, allergen-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.

Additional biomarker serum samples will be collected to study exploratory biomarkers of dupilumab activity and AD.

6.2.6. Future Biomedical Research

Biomarker samples will be collected at time points specified in section 6.1.

The biomarker samples unused for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of AD and other diseases. No additional samples will be collected for future biomedical research. After 15 years, any residual samples will be destroyed.

[REDACTED]

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 preexisting 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 admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events. See section [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 study reference manual 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 study reference manual for the procedure to be followed.

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

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

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

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

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,

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), by telephone within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 120 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE.

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

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Malignancy (except in situ carcinoma of the cervix, non-metastatic squamous or basal cell carcinoma of the skin)
- Helminthic infections
- Suicide-related events
- Any type of conjunctivitis or blepharitis (severe or serious or lasting ≥ 4 weeks)
- Keratitis

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

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

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 AE may have been caused by the study drug?

The possible answers are:

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

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

For a list of factors to consider in assessing the relationship of AEs to study drug, see [Appendix 1](#).

The 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 study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

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

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

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoint

The primary endpoint in the study is:

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

For the ex-US countries, the co-primary endpoints are:

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

8.2.2. Secondary Endpoints

The key secondary endpoints are:

- Proportion of patients with EASI-75 ($\geq 75\%$ improvement from baseline) at week 16 (this is not a secondary endpoint for ex-US countries as it is already a co-primary endpoint)
- Percent change in EASI score from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 3 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 16

Other secondary endpoints are:

- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Time to onset of effect on pruritus during the 16-week treatment period (≥ 3 point reduction of weekly average of peak Pruritus NRS from baseline)
- Time to onset of effect on pruritus during the 16-week treatment period (≥ 4 point reduction of weekly average of peak Pruritus NRS from baseline)
- 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 CDLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Percent change from baseline to week 4 in weekly average of daily peak Pruritus NRS
- Change from baseline to week 16 in HADS
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 4
- Incidence of skin-infection TEAEs (excluding herpetic infections) through week 16
- Incidence of serious TEAEs through week 16

8.2.3. Other Endpoints and Assessments

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

8.3. Pharmacokinetic Variables

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

8.4. Anti-Drug Antibody Variables

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

- Total number of patients negative in ADA assay at all time
- Total number of patients positive in ADA assay at any time
- Total number of patients with preexisting immunoreactivity – defined as either an ADA positive response in the assay at baseline with all postbaseline ADA results negative, or a positive response at baseline with all postbaseline ADA titer < 4 -fold over baseline titer level
- Total patients with treatment-emergent response – defined as a positive response in the ADA assay post first dose when baseline results are negative or missing.
- The treatment-emergent responses will be further characterized into the following categories:
 - Persistent ADA response – a treatment-emergent ADA positive response with 2 or more consecutive ADA positive sampling time points, separated by > 12 -week period (with no ADA negative samples in between)
 - Transient ADA response – a treatment-emergent ADA positive response that is not considered persistent or indeterminate

- Indeterminate ADA response – a treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay
- Total patients with treatment boosted response - defined as a positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive
- Titer value category
 - Low (titer <1,000)
 - Moderate ($1,000 \leq \text{titer} \leq 10,000$)
 - High (titer >10,000)

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

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

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

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

H0: No treatment difference between dupilumab and placebo

H1: There is a treatment difference between dupilumab and placebo

Baseline weight group (<60 kg and ≥ 60 kg) and disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) will be the 2 stratification factors for patient randomization and will be accounted for in the statistical modeling for efficacy.

9.2. Justification of Sample Size

It is estimated that with 80 patients per group, at the 2-sided 5% significance level, the study will have:

- 98% power to detect a difference of 28% between dupilumab Q2W treatment and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at week 16, assuming that the percentages are 37% and 9% for dupilumab Q2W and placebo, respectively.
- 88% power to detect a difference of 20% between dupilumab Q4W treatment and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at

week 16, assuming that the percentages are 29% and 9% for dupilumab Q4W and placebo, respectively.

- 99% power to detect a difference of 35% between dupilumab Q2W treatment and placebo treatment in the percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 48% and 13% for dupilumab Q2W and placebo, respectively.
- 99% power to detect a difference of 32% between dupilumab Q4W treatment and placebo treatment in percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 45% and 13% for dupilumab Q4W and placebo, respectively.

Additional power calculation based on the key secondary endpoint “proportion of patients with improvement (reduction) of Pruritus NRS ≥ 4 from baseline to week 16”, with 80 patients per group, the study will provide:

- 97% power at a 0.05 level to detect a difference of 27% in the percentages of patients achieving Pruritus NRS reduction ≥ 4 at week 16, assuming that the percentages are 38% and 11% for dupilumab Q2W and placebo, respectively.
- 95% power at a 0.05 level to detect a difference of 25% in the percentages of patients achieving weekly average of daily peak Pruritus NRS reduction ≥ 4 at week 16, assuming that the percentages are 36% and 11% for dupilumab Q4W and placebo, respectively.

The assumptions used for the power calculations were estimated based on results from the R668-AD-1334 and R668-AD-1416 studies (phase 3 studies for adult AD patients), and the R668-AD-1021 study (a phase 2b dose-ranging study in adults with AD). Based on the result from the R668-AD-1021 study, the efficacy profile of dupilumab 200 mg Q2W is similar to dupilumab 300 mg Q2W. In the absence of data of dupilumab in pediatric patients with AD, the data observed in the adult studies R668-AD-1334, R668-AD-1416, and R668-AD-1021 are used for these sample size calculations. This is a conservative assumption as it is expected that the effect of dupilumab in children will be greater than that seen in adults. Children have disease for a shorter duration than adults and the disease is more Th2 driven in acute phase while it becomes more type 1 helper T cell in chronic phase ([Thepen 1996](#), [Gittler 2012](#)). In addition, children with AD in general respond better to systemic therapies than adults ([Schmitt 2007](#)). A recent study compared the differences between activated and polarized T-cell subsets in blood of adult and pediatric patients with AD. The study found that AD is Th2 dominated in children while it extends to additional helper T cell subsets, particularly Th22, in adults ([Czarnowicki 2015](#)).

9.3. Analysis Sets

9.3.1. Efficacy Analysis Sets

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

The per protocol set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. A major protocol violation is one that may affect the interpretation of study results.

All efficacy variables will be evaluated on the FAS; the primary endpoint will also be evaluated on the PPS. Analysis on the FAS will be considered to be primary.

9.3.2. Safety Analysis Set

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

9.3.3. Pharmacokinetic Analysis Sets

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

9.3.4. Analysis Set for Anti-Drug Antibody Data

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

9.4. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation
- 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

9.5. Statistical Methods

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

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

9.5.1. Demography and Baseline Characteristics

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

9.5.2. Efficacy Analyses

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

9.5.2.1. Primary Efficacy Analysis

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

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

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

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

The Mantel-Fleiss (MF) criterion will be performed, and if it is not met while using the option CMH (MF) in SAS procedure PROC PREQ, sensitivity analyses including each factor separately in CMH test will be conducted. Sensitivity analysis using the last observation carried forward (LOCF) approach to determine patient's status at week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. The efficacy data will be set to missing after rescue treatment is used, then the LOCF method will be used to determine patients' status at week 16.

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

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 analysis.

For continuous endpoints:

- The multiple imputation (MI) with analysis of covariance (ANCOVA) model will be used as the primary analysis method. Patients' efficacy data through week 16 after the rescue treatment use will be set to missing first, and then be imputed by the multiple imputation method. Missing data from the FAS will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI following the 2 steps below:
 - Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345.
 - Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates including treatment groups, randomization strata (disease severity, weight group), and relevant baseline.

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

- To account for the impact of rescue treatment on the efficacy effect: If a patient receives rescue treatment, the efficacy data collected after rescue treatment is initiated will be treated as missing.
- In addition to the MI method described above, sensitivity analyses such as ANCOVA model with LOCF, MI method with ANCOVA model on all observed data regardless of rescue use will be conducted. Additional details on sensitivity analyses will be provided in the SAP.

9.5.2.3. Multiplicity Considerations

For multiplicity adjustment, a hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens versus placebo. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level.

The following is the preliminary plan for order of testing ([Table 3](#)). The final hierarchy will be provided in the SAP that will be finalized prior to database lock.

Table 3: Statistical Hierarchy for Multiplicity Control

		Dupilumab	
	Endpoints	q4w group	q2w group
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	10	1
Co-primary endpoint for ex-US countries, key secondary for US	Proportion of patients with EASI-75 ($\geq 75\%$ improvement from baseline) at week 16	9	2
Key Secondary endpoints	Percent change in EASI score from baseline to week 16	11	3
	Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS	12	4
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 3 from baseline to week 16	13	5
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 16	14	6
Secondary endpoints	Proportion of patients with EASI-50 at week 16	15	7
	Proportion of patients with EASI-90 at week 16	16	8
	Time to onset of effect on pruritus during the 16-week treatment period (≥ 3 point reduction of weekly average of peak Pruritus NRS from baseline)	25	17
	Time to onset of effect on pruritus during the 16-week treatment period (≥ 4 point reduction of weekly average of peak Pruritus NRS from baseline)	26	18
	Change from baseline to week 16 in percent BSA affected by AD	27	19
	Percent change from baseline to week 16 in SCORAD	28	20
	Change from baseline to week 16 in CDLQI	29	21
	Change from baseline to week 16 in POEM	30	22
	Change from baseline to week 16 in weekly average of daily peak Pruritus NRS	31	23
	Percent change from baseline to week 4 in weekly average of daily peak Pruritus	32	24
	Change from baseline to week 16 in HADS	35	33
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 from baseline to week 4	36	34
	Incidence of skin-infection TEAEs (excluding herpetic infections) through week 16	39	37
	Incidence of serious TEAEs through week 16	40	38

9.5.2.4. First-Step Analysis

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

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

9.5.3. Safety Analysis

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

9.5.3.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to end of study.

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

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

9.5.3.2. Other Safety

Vital Signs

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

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

Laboratory Tests

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

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

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

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

9.5.3.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment group and calculated as:

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

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

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

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

9.5.3.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

$$\text{Treatment Compliance} = (\text{Number of study drug injections during exposure period}) / (\text{Number of planned study drug injections during exposure period}) \times 100\%$$

The 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. Trough functional dupilumab concentration in serum ($C_{\text{trough, timepoint}}$) will be summarized at each time point using descriptive statistics. 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 Anti-Drug Antibody Data

The ADA variables described in section 8.4 will be summarized using descriptive statistics by treatment groups. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

9.5.6. Analysis of Biomarker Data

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

9.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

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

General rules for handling missing data:

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

Unscheduled assessments:

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

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:

- IVRS/IWRS system – randomization for sample collection schedules for dupilumab concentration and ADA, study drug supply
- EDC system – data capture
- SAS – statistical review, analysis, and reporting
- 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 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 within the EDC system by trained site personnel. All required electronic CRFs must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

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

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/IAFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

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 and applicable regulatory requirements.

13.2. Informed Consent

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

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

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

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

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

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

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

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 initials and a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF/IAF) must be kept in strict confidence.

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

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

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

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

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

14. PROTOCOL AMENDMENTS

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

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

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

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.

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY IN PATIENTS ≥ 12 TO < 18 YEARS OF AGE, WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS, Amendment 3, and agree to abide by all provisions set forth therein.

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

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

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

(Signature of Investigator)

(Date)

(Printed Name)

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

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

No:

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

Yes:

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

NOTE: This list is not exhaustive.

APPENDIX 2: IGA SCALE

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

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

Print Name (First/Last) of Investigator Completing

Assessment

Signature

Date

Instructions:

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

IGA: Disease Severity Scale and Definitions of the scoring:

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

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 randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥ 12 to < 18 years of age, with moderate-to-severe Atopic Dermatitis

Protocol Number: R668-AD-1526

Protocol Version: R668-AD-1526 Amendment 3

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

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