ORIGINAL ARTICLE

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

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ABSTRACT

BACKGROUND

Dupilumab, a human monoclonal antibody against interleukin-4 receptor alpha, inhibits signaling of interleukin-4 and interleukin-13, type 2 cytokines that may be important drivers of atopic or allergic diseases such as atopic dermatitis.

METHODS

In two randomized, placebo-controlled, phase 3 trials of identical design (SOLO 1 and SOLO 2), we enrolled adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment. Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment and a reduction of 2 points or more in that score from baseline at week 16.

RESULTS

We enrolled 671 patients in SOLO 1 and 708 in SOLO 2. In SOLO 1, the primary outcome occurred in 85 patients (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo (P<0.001 for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo (P<0.001 for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo (P<0.001 for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups.

CONCLUSIONS

In two phase 3 trials of identical design involving patients with atopic dermatitis, dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life, as compared with placebo. Trials of longer duration are needed to assess the long-term effectiveness and safety of dupilumab. (Funded by Sanofi and Regeneron Pharmaceuticals; SOLO 1 ClinicalTrials.gov number, NCT02277743; SOLO 2 ClinicalTrials.gov number, NCT02277769.)

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*A complete list of the SOLO 1 and SOLO 2 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Atopic dermatitis is a chronic, relapsing inflammatory skin disease that is characterized by the up-regulation of type 2 immune responses (including those involving type 2 helper T cells),[1,2] an impaired skin barrier, and increased *Staphylococcus aureus* colonization.[3,4] In patients with moderate-to-severe atopic dermatitis, skin lesions can encompass a large body-surface area and are frequently accompanied by intense, persistent pruritus, which leads to sleep deprivation, symptoms of anxiety or depression, and a poor quality of life.[5-7] For patients with moderate-to-severe atopic dermatitis, topical therapies have limited efficacy, and systemic treatments are associated with substantial toxic effects. Thus, there is an unmet need for effective and safe long-term medications for these patients.[8,9]

Dupilumab is a fully human monoclonal antibody that binds specifically to the shared alpha chain subunit of the interleukin-4 and interleukin-13 receptors, thereby inhibiting the signaling of interleukin-4 and interleukin-13, which are type 2 inflammatory cytokines that may be important drivers of atopic or allergic diseases such as atopic dermatitis and asthma.[10-14] In support of this premise, early-phase trials of dupilumab showed efficacy in patients with atopic dermatitis,[10,11,14,15] those with asthma,[16,17] and those with chronic sinusitis with nasal polyposis[18] — all of which are conditions that have type 2 immunologic signatures.[13] Clinical improvements were associated with improvement of inflammatory pathways, including type 2 pathways, and normalization of epidermal-barrier abnormalities.[10,11] Here we present the results of two phase 3 trials of dupilumab monotherapy (SOLO 1 and SOLO 2) in adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable.

Methods

Study Design and Oversight

We conducted two independent, randomized, double-blind, placebo-controlled, parallel-group trials of identical design to evaluate dupilumab in adults with moderate-to-severe atopic dermatitis in North America, Europe, and Asia. The two-trial concept was designed to provide replication of results. We enrolled patients from October 28, 2014, to July 8, 2015, in SOLO 1 and from December 3, 2014, to June 17, 2015, in SOLO 2. Data were not analyzed until after the statistical analysis plans were finalized on January 26, 2016.

Dupilumab or placebo was injected subcutaneously weekly or every other week for 16 weeks after a 35-day screening and washout period. Patients who were assigned to receive dupilumab every other week were given matching placebo on the off weeks in order to preserve the blinding (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were required to apply moisturizers twice daily for at least 7 consecutive days before randomization and throughout the trial period.

Topical or systemic rescue treatment to control unacceptable symptoms of atopic dermatitis could be used at the investigators' discretion. Dupilumab or placebo was discontinued in patients who received systemic rescue treatment.

During the treatment period, patients had weekly clinical and safety assessments and collection of blood samples. After the treatment period, eligible patients could enter an ongoing maintenance trial (LIBERTY AD SOLO-CONTINUE; ClinicalTrials.gov number, NCT02395133) or an open-label extension trial (LIBERTY AD MAINTAIN; NCT01949311). (Details about the follow-up studies are provided in the Supplementary Appendix.) For patients who were ineligible or unwilling to enter either trial, safety follow-up continued through week 28. The maintenance and open-label extension studies are not yet complete, so data from those studies are not included in this report.

These trials were conducted in accordance with the provisions of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted unblinded monitoring of patient safety. All the patients provided written informed consent before participation in the trial. The local institutional review board or ethics committee at each trial center oversaw trial conduct and documentation.

All the authors participated in interpretation of the data and provided input into the drafting of the manuscript, critical feedback, and final approval for submission of the manuscript for publication. The investigators had confidentiality agreements with the sponsors, Sanofi and Regeneron Pharma-

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ceuticals. Editorial support was provided by medical writers who were paid by the sponsors. The authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of the trials to the protocols, available at NEJM.org.

PATIENTS

Patients were eligible to participate in the trial if they were at least 18 years of age, had moderate-to-severe atopic dermatitis — including a score of 3 (moderate) or 4 (severe) on the Investigator's Global Assessment (IGA; scores range from 0 to 4, with higher scores indicating more severe disease) — for which topical treatment provided inadequate control or was medically inadvisable, and had chronic atopic dermatitis (according to the consensus criteria of the American Academy of Dermatology[19]) for at least 3 years before screening. (Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.)

TREATMENT

Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, weekly subcutaneous injections of dupilumab (300 mg) or placebo or the same dose of dupilumab every other week alternating with placebo. Patients in the dupilumab groups received a 600-mg loading dose of dupilumab on day 1. Randomization was conducted by means of a central interactive voice-response system and was stratified according to disease severity (IGA score, 3 vs. 4) and region. Blinded, coded kits containing dupilumab or placebo were used to mask the assigned treatment.

Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants. Rescue treatment for atopic dermatitis could be provided to patients if medically necessary (i.e., to control unacceptable symptoms of atopic dermatitis). If the rescue medication was topical, the patient could continue the assigned regimen; however, if the rescue medication was systemic (e.g., systemic glucocorticoids or nonsteroidal systemic immunosuppressive drugs), the trial regimen was immediately discontinued. (Detailed information about rescue treatment and prohibited concomitant medications is provided in the Supplementary Appendix.)

END POINTS

End points were analyzed according to a prespecified hierarchy (see the Statistical Analysis section). The primary end point was the proportion of patients with an IGA score of 0 or 1 (clear or almost clear)[20] and a reduction from baseline of at least 2 points in the score at week 16. The proportion of patients who had an improvement from baseline at week 16 of at least 75% on the Eczema Area and Severity Index (EASI-75) was a key secondary end point (and was identified as a coprimary end point by regulators in the European Union and Japan). The EASI score assesses the severity and extent of erythema; induration, papulation, and edema; excoriations; and lichenification.[21,22] EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of atopic dermatitis. (End-point descriptions are provided in Table S1 in the Supplementary Appendix.)

Other key secondary end points in the hierarchy were the proportions of patients with an improvement of at least 4 points at weeks 2, 4, and 16 or of at least 3 points at week 16 in the weekly average of peak scores for pruritus on a numerical rating scale that ranged from 0 to 10, with higher scores indicating more severe pruritus, and the mean percent change in the peak score on the numerical rating scale for pruritus from baseline to week 16.[23,24] Peak scores on the pruritus numerical rating scale were self-assessed by patients daily and were averaged over a week to create a weekly measurement; patients used an interactive voice-response system to record the peak score at screening and daily through week 16.

Additional secondary end points in the hierarchy were the mean percent change from baseline to week 16 on the EASI score, the Scoring Atopic Dermatitis (SCORAD) score,[25] and the Global Individual Signs Score (GISS) and the mean percent change from baseline to week 2 on the pruritus numerical rating scale; the proportion of patients with an improvement on the EASI of at least 50% (EASI-50) or at least 90% (EASI-90) at week 16; and the mean change from baseline to week 16 on the pruritus numerical rating scale, percent body-surface area affected, the score on the Dermatology Life Quality Index (DLQI),[26,27] the score on the Patient-Oriented Eczema Measure (POEM),[22,28] and the total score on the Hospital Anxiety and Depression Scale

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(HADS).[29,30] Additional prespecified end points were the proportion of patients with an improvement of at least 4 points (i.e., the minimal clinically important difference) from baseline to week 16 in the scores on the DLQI (scores range from 0 to 30, with higher scores indicating greater effect on quality of life) and the POEM (scores range from 0 to 28, with higher scores indicating a greater symptom burden) and the proportion of patients with HADS anxiety (HADS-A) and depression (HADS-D) subscores of less than 8 (on a scale from 0 to 21, with higher scores indicating a greater burden of anxiety or depression symptoms) at week 16 among patients who had had a baseline HADS-A or HADS-D subscore of 8 or more, which is the cutoff for identifying patients with anxiety or depression.[29] (A list of all efficacy end points is provided in the Supplementary Appendix.)

Over the 16-week treatment period, we evaluated safety outcomes, including adverse events, serious adverse events, and adverse events leading to treatment discontinuation. Adverse events were defined as the occurrence of any untoward medical condition during the treatment period.

STATISTICAL ANALYSIS

For binary outcomes, we used the Cochran–Mantel–Haenszel test after adjustment for randomization strata (disease severity and region). For the primary analysis of binary variables, we categorized data at time points after the use of rescue medication (either topical or systemic), withdrawal from the trial, or other missing data as indicating no response at all subsequent time points, including week 16. For continuous end points, we treated data that were collected after the use of rescue medication as missing, and subsequently we performed multiple imputation of missing data using the Markov-chain Monte Carlo algorithm and a regression model to generate multiple complete data sets at each time point. We then used analysis of covariance (ANCOVA) to evaluate data sets, with a model that included the assigned treatment, stratification factors (region and disease severity), and relevant baseline values. Results were then combined to generate statistical inferences.

We performed three prespecified sensitivity analyses for binary outcomes using the Cochran–Mantel–Haenszel test, with various methods to handle missing data. In the first sensitivity analysis, patients who had received rescue treatment or had withdrawn from the trial were considered to have had no response, and other missing values were imputed by means of the last-observation-carried-forward method. In the second sensitivity analysis, we included all observed values regardless of the use of rescue medication, with patients who had missing data treated as having had no response. In the third sensitivity analysis, we included all observed values regardless of the use of rescue medication, with no imputation of missing data.

We performed prespecified sensitivity analyses for continuous end points using the following methods to account for missing data: multiple imputation in which all observed data were included regardless of the use of rescue medication; use of a mixed-effect repeated-measures model, with data collected after the use of rescue medication treated as missing; treating data that were collected after the use of rescue medication as missing, followed by the last-observation-carried-forward method and ANCOVA; treating data that were collected after the use of rescue medication as missing, followed by the worst-observation-carried-forward method and ANCOVA; and ANCOVA on all observed values without imputation. (Additional statistical methods are provided in the Supplementary Appendix.)

To control for the overall type I error rate at 0.05 for primary and secondary end points across dose regimens, we used a significance level of 0.025 for comparisons of each dose of dupilumab with placebo according to the prespecified hierarchical order. If there were no significant between-group differences for a particular end point, testing would stop at that end point. All reported P values are two-sided. The significance of differences between dose groups was not investigated.

RESULTS

TRIAL PATIENTS

A total of 671 patients underwent randomization in SOLO 1 and 708 in SOLO 2 (Figs. S1 and S2 in the Supplementary Appendix). The randomized groups were well balanced with respect to baseline characteristics (Table 1, and Table S2 in the Supplementary Appendix). Approximately half of all patients had moderate atopic dermatitis (IGA score, 3), and half had severe atopic dermatitis (IGA score, 4). In each of the groups, a me-

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dian of approximately 50% of the patients' body-surface area was affected (Table 1). Before enrollment, 32.9% of the patients in SOLO 1 and 33.0% of those in SOLO 2 had received systemic glucocorticoids, and 25.9% and 31.4%, respectively, had received systemic immunosuppressant agents (Table S3 in the Supplementary Appendix).

PRIMARY OUTCOME

For both dupilumab regimens in the two trials, there were significant differences in all comparisons with placebo regarding the prespecified efficacy end points in the hierarchy (Table 2 and Figs. 1 and 2, and Figs. S4 through S7 in the Supplementary Appendix). At week 16, significantly more patients receiving dupilumab than receiving placebo had an IGA score of 0 or 1 and an improvement of 2 points or more on the IGA from the baseline score (primary end point). In SOLO 1, the primary outcome occurred in 85 patients (38%) receiving dupilumab every other week and in 83 (37%) receiving weekly dupilumab, as compared with 23 (10%) receiving placebo (P<0.001 for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) receiving dupilumab every other week and in 87 (36%) receiving weekly dupilumab, as compared with 20 (8%) receiving placebo (P<0.001 for both comparisons) (Table 2 and Fig. 1A).

CLINICAL SEVERITY

In the two trials, an improvement of at least 75% on the EASI (EASI-75) at week 16 was reported in significantly more patients receiving each regimen of dupilumab than among those receiving placebo (P<0.001 for all comparisons) (Table 2 and Fig. 1B). The least-squares mean (±SE) percent change in the EASI score from baseline to week 16 was significantly greater among patients receiving dupilumab than among those receiving placebo, with reductions of 72.3±2.6 among those receiving dupilumab every other week and 72.0±2.6 among those receiving weekly dupilumab, as compared with a reduction of 37.6±3.3 among those receiving placebo in SOLO 1; there were least-squares mean percent reductions of 67.1±2.5, 69.1±2.5, and 30.9±3.0, respectively, in SOLO 2 (P<0.001 for all comparisons) (Table 2 and Fig. 2A and 2B). Results in the two dupilumab groups in the two trials were significantly better than those in the placebo groups in additional measures of clinical severity, including EASI-50, EASI-90, body-surface area affected, and scores on SCORAD and GISS (P<0.001 for all comparisons) (Table 2).

MEASURES OF PRURITUS

At week 16, an improvement of at least 3 points or at least 4 points in the peak score on the pruritus numerical rating scale occurred in significantly more patients receiving dupilumab than in those receiving placebo (P<0.001 for all comparisons) (Table 2). By week 2, patient-reported scores with respect to itching were significantly better among patients receiving dupilumab than among those receiving placebo (Table 2 and Fig. 2C and 2D).

PATIENT-REPORTED SYMPTOMS AND QUALITY OF LIFE

In the two trials, dupilumab significantly reduced patient-reported symptoms of atopic dermatitis and its effect on sleep, symptoms of anxiety or depression, and quality of life (Table 2, and Table S4 and Figs. S6 and S7 in the Supplementary Appendix). For both the DLQI and POEM scores, significantly more patients in the two dupilumab groups than in the placebo groups had a reduction of at least 4 points (considered to be the minimal clinically important difference[22,27]) in the total score (Table S4 in the Supplementary Appendix). Among patients who had had symptoms of anxiety or depression (HADS-A or HADS-D score, ≥8) at baseline, significantly more dupilumab-treated patients than those receiving placebo had HADS-A and HADS-D scores of less than 8 at week 16 (Table S4 in the Supplementary Appendix).

USE OF RESCUE MEDICATION

In the two trials, more patients in the placebo group than in either dupilumab group received rescue treatment. In SOLO 1, the rates of rescue treatment were 21% among those receiving dupilumab every other week and 23% among those receiving dupilumab every week, as compared with 51% among those receiving placebo; in SOLO 2, the rates were 15%, 21%, and 52%, respectively (Table S5 in the Supplementary Appendix). Patients in the placebo groups were more likely to receive systemic rescue therapies (glucocorticoids or immunosuppressant agents) (Table S5 in the Supplementary Appendix) and tended to receive rescue treatments earlier than dupilumab-treat-

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	SOLO 1			SOLO 2		
	Placebo (N = 224)	Dupilumab Every Other Week (N = 224)†	Dupilumab Every Week (N = 223)	Placebo (N = 236)	Dupilumab Every Other Week (N = 233)†	Dupilumab Every Week (N = 239)
Median age (IQR) — yr	39.0 (27.0–50.5)	38.0 (27.5–48.0)	39.0 (27.0–51.0)	35.0 (25.0–47.0)	34.0 (25.0–46.0)	35.0 (25.0–46.0)
Male sex — no. (%)	118 (53)	130 (58)	142 (64)	132 (56)	137 (59)	139 (58)
Race — no. (%)‡						
White	146 (65)	155 (69)	149 (67)	156 (66)	165 (71)	168 (70)
Black	16 (7)	10 (4)	20 (9)	20 (8)	13 (6)	15 (6)
Asian	56 (25)	54 (24)	51 (23)	50 (21)	44 (19)	45 (19)
Other or missing data	6 (3)	5 (2)	3 (1)	10 (4)	11 (5)	11 (5)
Median disease duration (IQR) — yr	28.0 (19.0–40.0)	26.0 (17.0–40.0)	26.0 (16.0–42.0)	26.0 (18.0–39.0)	24.5 (18.0–36.0)	24.0 (17.0–37.0)
Median affected body-surface area (IQR) — %	57.0 (37.4–77.0)	53.4 (37.4–72.5)	54.5 (39.0–73.0)	53.3 (34.0–72.8)	50.0 (36.0–68.0)	50.0 (34.0–69.0)
Median EASI score (IQR)§	31.8 (22.2–43.8)	30.4 (21.5–40.8)	29.8 (22.0–41.2)	30.5 (22.1–41.7)	28.6 (21.0–40.1)	29.0 (21.2–41.8)
IGA score of 4 — no. (%)¶	110 (49)	108 (48)	106 (48)	115 (49)	115 (49)	112 (47)
Median peak score on numerical rating scale for pruritus (IQR)‖	7.7 (6.2–8.6)	7.6 (5.9–8.7)	7.7 (6.0–8.7)	7.7 (6.5–9.0)	7.8 (6.7–8.9)	7.8 (6.3–8.9)
Median total SCORAD score (IQR)**	67.0 (58.0–77.6)	65.1 (56.5–77.4)	65.9 (57.2–75.8)	68.9 (58.6–78.5)	67.8 (57.3–76.7)	67.4 (58.4–77.9)
Median POEM score (IQR)††	21.0 (16.0–25.0)	21.0 (16.0–25.0)	22.0 (17.0–26.0)	23.0 (17.0–26.0)	21.0 (18.0–25.0)	21.0 (18.0–26.0)
Median DLQI score (IQR)‡‡	14.0 (9.0–20.0)	13.0 (8.0–19.0)	14.0 (8.0–20.0)	15.0 (9.0–22.0)	15.0 (10.0–21.0)	16.0 (10.0–22.0)
Median total HADS score (IQR)§§	12.0 (6.0–17.0)	11.0 (6.0–17.0)	12.0 (6.0–17.5)	12.0 (7.0–19.0)	13.0 (8.0–19.0)	14.0 (8.0–20.0)
HADS-A or HADS-D score ≥8 — no. (%)§§	97 (43)	100 (45)	102 (46)	115 (49)	129 (55)	136 (57)
Median GISS score (IQR)¶¶	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–11.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
Previous history of eczema herpeticum — no. (%)	4 (2)	4 (2)	6 (3)	3 (1)	7 (3)	0

* There were no significant differences between the dupilumab groups and the placebo groups in any of the listed categories. IQR denotes interquartile range. Percentages may not total 100 because of rounding.

† In this regimen, dupilumab was administered every other week and placebo every other week to maintain blinding.

‡ The protocol did not specify how data on race should be collected.

§ Scores on the Eczema Area and Severity Index (EASI) range from 0 to 72, with higher scores indicating greater severity; a change of 6.6 has been estimated as the minimal clinically important difference (MCID).

¶ Scores on the Investigator's Global Assessment (IGA) scale range from 0 to 4, with higher scores indicating greater severity; the MCID for this scale has not been determined.

‖ The peak score on the numerical rating scale for pruritus is a patient-reported measure that assesses the maximum itch intensity in the previous 24 hours on a scale ranging from 0 to 10, with higher values indicating worse itching.

** Scoring Atopic Dermatitis (SCORAD) is a combined score of investigator-reported disease severity and affected body-surface area and patient-reported symptoms of itch and sleep dysfunction; scores range from 0 to 103, with higher scores indicating greater severity; a change of 8.7 has been estimated as the MCID.

†† The Patient-Oriented Eczema Measure (POEM), a composite measure of patient-reported symptoms including the effect of symptoms on sleep, evaluates the frequency of symptoms (including itching) and the effect of atopic dermatitis on sleep on a scale of 0 to 28, with higher scores indicating greater severity; a change of 4 has been estimated as the MCID.

‡‡ The Dermatology Life Quality Index (DLQI) evaluates health-related quality of life on a scale of 0 to 30, with higher scores indicating greater effect on quality of life. A change of 4 has been estimated as the MCID.

§§ The Hospital Anxiety and Depression Scale (HADS) measures patient-reported symptoms of anxiety and depression on a scale from 0 to 42; scores on HADS-A (measuring anxiety) and HADS-D (measuring depression) subscales range from 0 to 21, with higher scores indicating a greater burden of anxiety or depression symptoms; the MCID for this scale has not been determined. The recommended cutoff score for identifying patients with anxiety or depression is 8.

¶¶ The Global Individual Signs Score (GISS) is a cumulative score of ratings for individual components of lesions associated with atopic dermatitis (erythema, infiltration or papulation, excoriations, and lichenification); the cumulative score ranges from 0 to 12, with higher scores indicating greater severity; the MCID for this scale has not been determined.

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ed patients (Fig. S3 in the Supplementary Appendix).

Overall, among patients receiving dupilumab, similar results were observed in the primary analysis and with all observed values regardless of the use of rescue medication (Figs. S4 and S5 in the Supplementary Appendix). Outcomes of sensitivity analyses were similar to those of the primary analysis (Table S6 in the Supplementary Appendix).

SAFETY

The overall incidence of adverse events was similar in the dupilumab groups and the placebo groups in the two trials (Table 3). Serious adverse events and adverse events leading to treatment discontinuation were uncommon in the two trials (Table 3, and Tables S7 and S8 in the Supplementary Appendix). The only serious adverse event that was reported in more than 2 patients in any treatment group was a serious exacerbation of atopic dermatitis, which was reported in 2 patients receiving dupilumab every other week and 3 receiving placebo in SOLO 1 and in 1 patient receiving weekly dupilumab and 5 patients receiving placebo in SOLO 2 (Table S7 in the Supplementary Appendix).

Adverse events that were categorized as "infections and infestations" in the *Medical Dictionary for Regulatory Activities* (MedDRA) system organ class (which includes any type of infectious adverse event, regardless of cause or organ system) developed in 35% of the patients receiving dupilumab every other week and in 34% of those receiving dupilumab every week, as compared with 28% of those receiving placebo in SOLO 1 and in 28%, 29%, and 32%, respectively, in SOLO 2. (Common adverse events that are categorized as MedDRA preferred terms in this class included nasopharyngitis, upper respiratory tract infection, and conjunctivitis, including conjunctivitis of unspecified cause.) Skin infections were observed in 6% of patients receiving each dose of dupilumab in the two trials and in 8% of those receiving placebo in SOLO 1 and 11% in SOLO 2. All "infections and infestations" that were not reported as skin infections could be classified as "non-skin" infections; these were reported in 30% of the patients receiving dupilumab every other week, in 31% of those receiving dupilumab every week, and in 22% of those receiving placebo in SOLO 1 and in 25%, 26%, and 24%, respectively, in SOLO 2 (Table 3, and Table S9 in the Supplementary Appendix). Herpes infections were reported in 7%, 4%, and 4% of patients, respectively, in SOLO 1 and in 4%, 5%, and 3% of patients, respectively, in SOLO 2 (Table 3, and Table S9 in the Supplementary Appendix). Additional details regarding serious, severe, and opportunistic infections are provided in Table S10 in the Supplementary Appendix.

There were two deaths in SOLO 2: a 49-year-old woman who was not receiving an asthma-control medication died of an asthma attack 84 days after the last dose of dupilumab, and a 31-year-old man with a history of depression, including hospitalization for depression, and suicidal ideation committed suicide, an event that occurred 8 days after the most recent dose of dupilumab. (Detailed narratives are provided in the Supplementary Appendix.)

The most common adverse events in the two trials were exacerbations of atopic dermatitis, injection-site reactions, and nasopharyngitis (Table 3). The incidence of nasopharyngitis was generally balanced across dupilumab and placebo groups. Dupilumab-treated patients had a higher incidence of injection-site reactions, most of which were mild or moderate. Exacerbations of atopic dermatitis and most types of skin infections were more common in the placebo groups. The rates of conjunctivitis with an unspecified cause and allergic conjunctivitis were higher in the dupilumab groups than in the placebo groups (Table 3); bacterial or viral conjunctivitis (MedDRA preferred term) was reported in less than 2% of the patients in any group (Table S9 in the Supplementary Appendix).

Laboratory values, vital signs, and electrocardiographic assessments did not indicate noteworthy differences among treatment groups. Small transient increases in eosinophil levels from baseline were observed in the dupilumab groups at weeks 4 and 8, with subsequent decreases toward or below baseline levels by week 16 (Table S11 and Fig. S8 in the Supplementary Appendix).

DISCUSSION

In SOLO 1 and SOLO 2, both dose regimens of dupilumab resulted in better results than placebo over 16 weeks of treatment across multiple outcome measures that reflected objective signs of atopic dermatitis, subjective symptoms (e.g., pruritus), important aspects of mental

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Table 2. Efficacy Outcomes.*

Outcome	SOLO 1†			SOLO 2†		
	Placebo (N = 224)	Dupilumab Every Other Week (N = 224)	Dupilumab Every Week (N = 223)	Placebo (N = 236)	Dupilumab Every Other Week (N = 233)	Dupilumab Every Week (N = 239)
IGA score of 0 or 1 and reduction of ≥2 points from baseline at week 16: primary outcome — no. (%)	23 (10)	85 (38)	83 (37)	20 (8)	84 (36)	87 (36)
Key secondary outcomes						
EASI-75 at wk 16 — no. (%)‡	33 (15)	115 (51)	117 (52)	28 (12)	103 (44)	115 (48)
Least-squares mean percent change from baseline in peak score on numerical rating scale for pruritus at wk 16	−26.1±3.0	−51.0±2.5	−48.9±2.6	−15.4±3.0	−44.3±2.3	−48.3±2.4
Improvement in peak score on numerical rating scale for pruritus — no./total no. (%)						
≥4 points from baseline to wk 16§	26/212 (12)	87/213 (41)	81/201 (40)	21/221 (10)	81/225 (36)	89/228 (39)
≥3 points from baseline to wk 16 ¶	38/221 (17)	103/220 (47)	109/211 (52)	29/226 (13)	117/231 (51)	115/234 (49)
≥4 points from baseline to wk 4§	13/212 (6)	34/213 (16)‖	47/201 (23)	14/221 (6)	51/225 (23)	63/228 (28)
≥4 points from baseline to wk 2§	7/212 (3)	20/213 (9)**	19/201 (9)††	2/221 (1)	24/225 (11)	29/228 (13)
Other secondary outcomes						
Peak least-squares mean change from baseline in peak score on numerical rating scale for pruritus at wk 16	−2.03±0.21	−3.78±0.16	−3.72±0.17	−1.21±0.22	−3.30±0.16	−3.68±0.16
Least-squares mean percent change from baseline in EASI score at wk 16	−37.6±3.3	−72.3±2.6	−72.0±2.6	−30.9±3.0	−67.1±2.5	−69.1±2.5
EASI-50 at wk 16 — no. (%)	55 (25)	154 (69)	136 (61)	52 (22)	152 (65)	146 (61)
EASI-90 at wk 16 — no. (%)	17 (8)	80 (36)	74 (33)	17 (7)	70 (30)	73 (31)
Least-squares mean change from baseline in affected body-surface area at wk 16	−15.4±1.9	−33.4±1.4	−34.3±1.4	−12.6±1.6	−30.6±1.3	−32.1±1.3
Least-squares mean percent change from baseline in SCORAD score at wk 16	−29.0±3.2	−57.7±2.1	−57.0±2.1	−19.7±2.5	−51.1±2.0	−53.5±2.0
Least-squares mean change from baseline in DLQI score at wk 16	−5.3±0.5	−9.3±0.4	−9.0±0.4	−3.6±0.5	−9.3±0.4	−9.5±0.4
Least-squares mean change from baseline in POEM score at wk 16	−5.1±0.7	−11.6±0.5	−11.0±0.5	−3.3±0.6	−10.2±0.5	−11.3±0.5
Least-squares mean change from baseline in HADS total score at wk 16	−3.0±0.7	−5.2±0.5	−5.2±0.5	−0.8±0.4	−5.1±0.4	−5.8±0.4
Least-squares mean percent change from baseline in GISS score at wk 16	−26.4±3.3	−53.4±2.4	−52.0±2.4	−17.9±2.5	−45.6±2.1	−46.8±2.1
Least-squares mean percent change from baseline in peak score on numerical rating scale for pruritus at wk 2	−3.5±1.8	−19.9±1.7	−18.5±1.7	−5.3±1.6	−23.1±1.6	−20.3±1.6

* Plus–minus values are means ±SE. Unless otherwise indicated, efficacy analyses were performed in the full analysis set, which included all patients who underwent randomization. Within each dose regimen, the primary and secondary end points were tested with a hierarchical testing procedure with a prespecified order — in other words, inferential conclusions about successive end points required statistical significance of the previous end point at a 0.025 significance level. Most outcomes were assessed at scheduled trial visits.

† Unless otherwise indicated, P<0.001 for the comparison between each regimen of dupilumab and placebo.

‡ The EASI-75 at week 16 was the coprimary outcome in the European Union and Japan.

§ Included in this analysis were patients with a baseline peak score of at least 4 on the numerical rating scale for pruritus.

¶ Included in this analysis were patients with a baseline peak score of at least 3 on the numerical rating scale for pruritus.

‖ P=0.001 versus placebo.

** P=0.010 versus placebo.

†† P=0.009 versus placebo.

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health (i.e., anxiety and depression), and quality of life. The mean efficacy results were similar for both dupilumab regimens. SOLO 1 and SOLO 2 were designed to provide replication of results, and patient populations and results were highly consistent in the two trials.

Our findings confirm and expand on the results of previous early-phase trials of dupilumab in patients with moderate-to-severe atopic dermatitis.[10,11,14,15] Improvement in the primary outcome was supported by improvement in all other measures of clinical severity and extent of involvement. The between-group difference was significant for all prespecified efficacy end points that were listed in the statistical hierarchy. In addition, significant improvement was observed with respect to patient-reported symptoms of atopic dermatitis (including the effect on pruritus and sleep), symptoms of anxiety or depression, and health-related quality of life, with a significant reduction in itching apparent by week 2. These data suggest that the amelioration of signs and symptoms of atopic dermatitis by treatment with dupilumab may reduce the disease burden associated with moderate-to-severe atopic dermatitis across multiple domains that are important to patients.

Sensitivity analyses showed that the primary efficacy outcome was not driven by the categorization of the use of rescue medication as no response. Indeed, the between-group difference in this outcome remained significant when patients who received rescue medication were included in the analysis, even though considerably more patients in the placebo groups than in the dupilumab groups received rescue treatment.

The incidence of conjunctivitis was higher among patients receiving dupilumab than among those receiving placebo. The cause of conjunctivitis in patients with atopic dermatitis is not yet fully understood. In contrast to our findings in the current trials, the incidence of conjunctivitis was not increased in dupilumab-treated patients in early studies of dupilumab involving patients with asthma[16,17] or with chronic sinusitis with nasal polyposis,[18] which suggests that characteristics specific to atopic dermatitis may contribute to its cause. Further studies on the causes of conjunctivitis are warranted.

In phase 1 and phase 2a studies of dupilumab in patients with moderate-to-severe atopic dermatitis, the most frequent serious adverse events were exacerbation of atopic dermatitis and skin infections, both of which were more frequent in the placebo groups, whereas in the phase 2b trial, there was no apparent imbalance in the rates of serious adverse events across treatment groups.[10,14] In SOLO 1 and SOLO 2, infections were reported in 28 to 35% of patients receiving dupilumab and in 28 to 33% of those receiving placebo. Her-

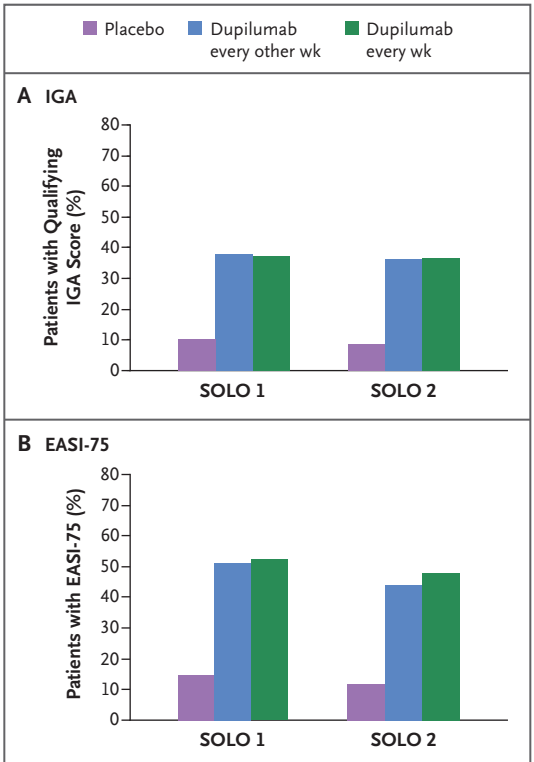


Figure 1. Primary End Point and Key Secondary End Point.

Panel A shows the proportions of patients with the primary end point (both a score of 0 or 1 [clear or almost clear] on the Investigator's Global Assessment [IGA; scores range from 0 to 4, with higher scores indicating more severe disease] and a reduction from baseline of 2 points or more on the IGA at week 16) among patients who received dupilumab every week, dupilumab every other week, or placebo in SOLO 1 and SOLO 2. Panel B shows the proportions of patients with the key secondary end point (which was considered to be a coprimary end point by regulators in the European Union and Japan) of an improvement from baseline of at least 75% on the Eczema Area and Severity Index (EASI-75) at week 16 in the two trials. P<0.001 for all comparisons between dupilumab and placebo. For binary end points, patients who received rescue medications or withdrew from the study were categorized as having had no response, as were those with all other missing values.

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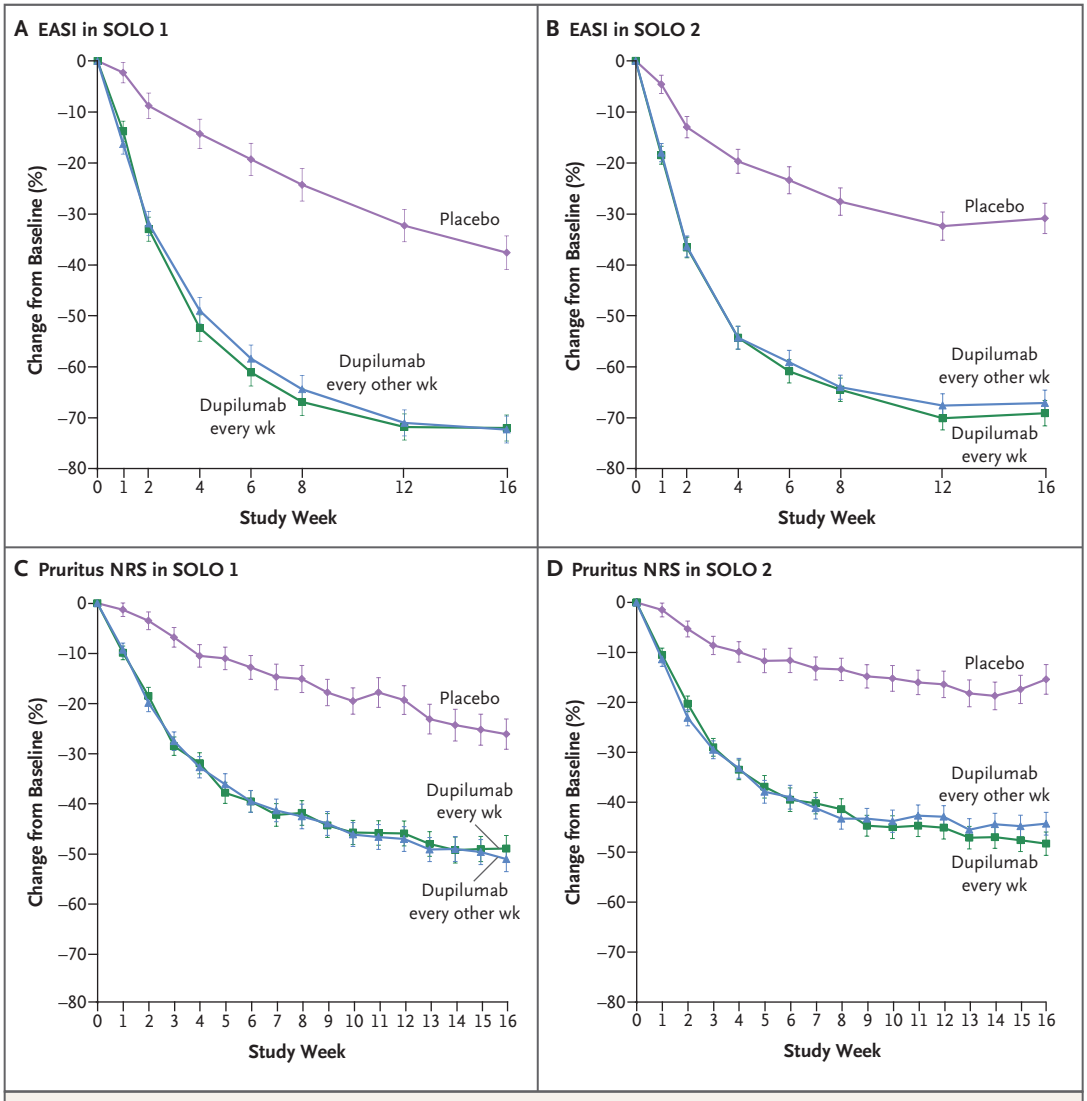


Figure 2. Secondary End Points.

Shown are the least-squares mean percent changes from baseline in the Eczema Area and Severity Index (EASI) score (Panels A and B) and in the weekly average of peak scores on the numerical rating scale (NRS) for pruritus (a key secondary end point) (Panels C and D) in SOLO 1 and SOLO 2 at 16 weeks ($P<0.001$ for all comparisons with placebo). The I bars represent standard errors. For the pruritus NRS, the baseline peak score was the average of the daily scores for maximum itch intensity during the 7 days immediately preceding randomization (minimum of four scores required). For continuous end points, data from patients who received rescue medications were categorized as missing at all time points after the receipt of the rescue medication; missing data were imputed with the use of a multiple-imputation method.

pes viral infections of any type were reported in 4 to 7% of patients receiving dupilumab and in 3 to 4% of those receiving placebo. The patients receiving placebo had a higher incidence of skin infections (8 to 11%) than did dupilumab-treated patients (approximately 6%), a finding that was consistent with an improvement in skin-barrier integrity and function associated with dupilumab,[10,11] whereas non-skin infections were observed in 25 to 31% of patients receiving dupilumab and in 22 to 24% of those receiving placebo. There is evidence that reducing type 2 skin inflammation helps normalize skin antimicrobial responses.[31-36] Two deaths were reported in the dupilumab groups. These trials were not long enough or large enough to exclude uncom-

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Table 3. Adverse Events.*

Event	SOLO 1			SOLO 2		
	Placebo (N = 222)	Dupilumab Every Other Week (N = 229)	Dupilumab Every Week (N = 218)	Placebo (N = 234)	Dupilumab Every Other Week (N = 236)	Dupilumab Every Week (N = 237)
	number of patients (percent)					
Adverse or serious adverse event						
At least 1 adverse event	145 (65)	167 (73)	150 (69)	168 (72)	154 (65)	157 (66)
At least 1 serious adverse event	11 (5)	7 (3)	2 (1)	13 (6)	4 (2)	8 (3)
Death†	0	0	0	0	1 (<1)	1 (<1)
Adverse event leading to treatment discontinuation	2 (1)	4 (2)	4 (2)	5 (2)	2 (1)	3 (1)
Noninfectious adverse event‡						
Injection-site reaction	13 (6)	19 (8)	41 (19)	15 (6)	32 (14)	31 (13)
Exacerbation of atopic dermatitis	67 (30)	30 (13)	21 (10)	81 (35)	32 (14)	38 (16)
Headache	13 (6)	21 (9)	11 (5)	11 (5)	19 (8)	22 (9)
Allergic conjunctivitis	2 (1)	12 (5)	7 (3)	2 (1)	2 (1)	3 (1)
Infectious adverse event‡						
Infections and infestations§	63 (28)	80 (35)	74 (34)	76 (32)	65 (28)	68 (29)
Nasopharyngitis	17 (8)	22 (10)	25 (11)	22 (9)	20 (8)	20 (8)
Upper respiratory tract infection	5 (2)	6 (3)	11 (5)	5 (2)	7 (3)	9 (4)
Conjunctivitis¶	2 (1)	11 (5)	7 (3)	1 (<1)	9 (4)	9 (4)
Any herpes viral infection‖	9 (4)	15 (7)	9 (4)	8 (3)	10 (4)	12 (5)
Oral herpes	4 (2)	9 (4)	4 (2)	4 (2)	8 (3)	9 (4)
Herpes simplex	3 (1)	7 (3)	2 (1)	1 (<1)	0	1 (<1)
Eczema herpeticum	2 (1)	1 (<1)	1 (<1)	1 (<1)	2 (1)	0
Herpes virus infection	0	0	1 (<1)	1 (<1)	0	0
Herpes zoster	1 (<1)	1 (<1)	0	1 (<1)	0	0
Ophthalmic herpes simplex	0	0	1 (<1)	0	0	0
Genital herpes	1 (<1)	0	0	0	0	1 (<1)
Herpes ophthalmic	0	0	0	1 (<1)	0	1 (<1)
Herpes simplex otitis externa	0	0	0	0	1 (<1)	0
Adjudicated skin infection	18 (8)	13 (6)	14 (6)	26 (11)	13 (6)	15 (6)
Non-skin infection	49 (22)	69 (30)	67 (31)	57 (24)	58 (25)	61 (26)

* Patients are listed according to the study drug received, which may differ from the randomized group. Adverse events that were reported at the level of preferred terms occurred in at least 5% of the patients in any randomized group, with the exception that all adverse events with preferred terms related to herpes virus infection are reported here. Included in the safety analysis were all the patients who underwent randomization and received at least one dose of dupilumab or placebo.

† Details regarding the two deaths are provided in the Supplementary Appendix.

‡ Adverse events are reported at the preferred term level of the *Medical Dictionary for Regulatory Activities* (MedDRA) hierarchy, unless otherwise indicated.

§ This adverse event is reported at the system organ class level in the MedDRA hierarchy.

¶ This MedDRA preferred term includes conjunctivitis of unspecified cause.

‖ This adverse event is reported at the high-level term in the MedDRA hierarchy.

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mon adverse events, and results from larger studies of longer duration are needed to assess the effectiveness and safety of long-term treatment with dupilumab.

Patients with atopic dermatitis, particularly moderate-to-severe disease, are at increased risk for depression.[37,38] Five patients had various serious adverse events related to depression (four in the placebo group and one in the group receiving weekly dupilumab); of these patients, one in the dupilumab group committed suicide. Symptoms of anxiety or depression were reduced to a significantly greater extent with dupilumab than with placebo among patients who had these symptoms at baseline (Table S4 in the Supplementary Appendix). These data underscore the substantial psychosocial effect of moderate-to-severe atopic dermatitis on quality of life and aspects of mental health and the potential for improvement in these areas associated with amelioration of the signs and symptoms of atopic dermatitis with dupilumab.

These trials have several limitations. First, neither trial was planned to allow statistical separation of the two doses of dupilumab. However, in each trial, the two regimens showed similar efficacy and safety. Second, the 16-week treatment period did not address efficacy and safety of longer-term treatment. Third, concomitant topical glucocorticoids and calcineurin inhibitors were allowed only as rescue therapy; another phase 3 trial (LIBERTY AD CHRONOS) has evaluated the efficacy and safety of dupilumab with concomitant topical glucocorticoids with or without topical calcineurin inhibitors.[39] Fourth, we evaluated dupilumab in adults, but not children, in whom atopic dermatitis is more prevalent. A recently completed study evaluated the pharmacokinetics and preliminary efficacy and safety of dupilumab in children.

These results show that the type 2 cytokines interleukin-4 and interleukin-13 are key drivers of atopic dermatitis; they further support the possibility, suggested by earlier studies in related diseases, that interleukin-4 and interleukin-13 are important drivers of atopic or allergic diseases in general, including asthma and chronic sinusitis with nasal polyposis.[16-18]

In conclusion, in two phase 3 trials of identical design involving patients with moderate-to-severe atopic dermatitis that was inadequately controlled with topical medications, both regimens of dupilumab (every other week and weekly) were superior to placebo in ameliorating the signs and symptoms of atopic dermatitis (including pruritus and the effect on sleep), causing clinically meaningful reductions in patient-reported symptoms of anxiety and depression, and improving health-related quality of life. Injection-site reactions and conjunctivitis were more frequent in patients receiving dupilumab than in those receiving placebo. The results of these trials confirm and extend findings on dupilumab from earlier studies involving patients with moderate-to-severe atopic dermatitis.[10,14,15]

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APPENDIX

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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. DOI: 10.1056/NEJMoa1610020

This supplement contains the following items:

1. SOLO 1 ……Pg. 2
    a. Original protocol, final protocol, summary of changes
    b. Original statistical analysis plan, final statistical analysis plan, summary of changes

2. SOLO 2 ……Pg. 309
    a. Original protocol, final protocol, summary of changes
    b. Original statistical analysis plan, final statistical analysis plan, summary of changes

SOLO 1

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Protocol: original

Protocol: final

Amendment 2 (05 Feb 2015)

Amendment 1 (10 Nov 2014)

Statistical analysis plan: original

Statistical analysis plan: final

Modifications from the Statistical Plan in the Final Protocol

Modifications from the Previously Approved SAP

Clinical Study Protocol

A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Compound:	Dupilumab
Study Name:	Liberty AD Solo
Clinical Phase:	3
Protocol Number:	R668-AD-1334
Date of Issue:	08 AUG 2014
Scientific/Medical Monitor:	Marius Ardeleanu, MD Senior Director, Clinical Sciences Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis
Site Location(s)	Global
Principal Investigator	Not Applicable
Objective(s)	The primary objective is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe atopic dermatitis (AD). The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD.
Study Design	This is a randomized, double-blind, placebo-controlled, parallel group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28-weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below). After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 to receive once weekly (qw) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, every 2 weeks (q2w) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global

	Assessment (IGA) = 3] vs. severe [IGA = 4] AD) and by region. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic. During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits. The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoints will be determined at week 16. Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not been rescued will be eligible to participate in a maintenance study. Patients who meet these criteria but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20: • patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab • patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 to 4 (whichever comes first). For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28. Safety, laboratory, and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events.
Study Duration	Each patient's participation in the study will be up to approximately 21 weeks or 33 weeks, including the screening period.

Population	
Sample Size:	Approximately 600 patients will be enrolled at approximately 160 global study sites
Target Population:	The study population includes adults 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)
Treatment(s)	
Study Drug Dose/Route/Schedule:	Dupilumab SC Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg dupilumab in a 2 mL volume) on day 1 followed by 300 mg in 2 mL qw from week 1 through week 15 Or Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg in a 2 mL volume) on day 1 followed by 300 mg in 2 mL q2w from week 1 through week 15. The last dose of study drug for both regimens will be at week 15.
Placebo Route/Schedule:	Matching placebo SC injection. Loading dose for the placebo arm consists of 2 injections, each containing placebo formulation in a 2 mL volume, administered at day 1 and followed by qw injections of 2 mL placebo formulation from week 1 through week 15 (last dose of study drug will be at week 15).
Endpoint(s)	During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries.
Primary:	• Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
Co-Primary for European Medicines Agency (EMA) and EMA Reference Market Countries Submissions:	• Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 • Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
Secondary:	• Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA as it is already a co-primary endpoint)

	• Percent change from baseline to week 16 in pruritus numerical rating scale (NRS) • Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16 • Percent change in EASI score from baseline to week 16 • Change from baseline to week 16 in percent Body Surface Area (BSA) • Change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD) • Change from baseline to week 16 in Global Individual Signs Score (GISS) (erythema, infiltration/population, excoriations, lichenification) • Change from baseline to week 16 in Dermatology Life Quality Index (DLQI) • Change from baseline to week 16 in Hospital Anxiety Depression Scale (HADS) • Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM) • Percent change from baseline to week 2 in pruritus NRS • Incidence of skin infection treatment-emergent adverse events (TEAE) requiring systemic treatment from baseline through week 16 • Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16 • Incidence of TEAEs leading to treatment discontinuation from baseline through week 16 • Overall incidence of TEAEs through week 16
Procedures and Assessments	A variety of parameters will be collected during the study to assess the efficacy of dupilumab, including measures of AD severity, and patient-reported measures of AD symptoms and quality of life (QOL). The safety of dupilumab in this population will be assessed by evaluating TEAEs, detailed medical history, thorough physical examination, vital signs, electrocardiograms (ECGs), and clinical laboratory testing. Concomitant medications and procedures will be collected from time of informed consent to the end of the study. Safety data will be reviewed on an ongoing basis by the sponsor. An independent data monitoring committee (IDMC) that oversees the entire dupilumab clinical development program will review safety data periodically in an unblinded fashion and will advise the sponsor

	of potential safety signals. Blood samples will be collected for dupilumab concentration and anti-dupilumab antibody (ADA) levels at pre-determined time points. Research samples and samples for exploratory biomarker analysis will be collected.
Statistical Plan	**Sample Size:** To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total with a randomization ratio of 1:1:1 dupilumab, 300 mg qw: 300 mg q2w: placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment) to detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively. The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively. The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. **Efficacy Analysis Set:** The full analysis set (FAS) includes all randomized patients who receive any study medication. Efficacy analysis will be based on treatment allocated at randomization (as randomized), which will be stratified by disease severity and region. **Methods:** For continuous variables, descriptive statistics will include: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category. 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.

Primary Efficacy Analysis

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

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, a mixed-effect model with repeated measures (MMRM) will be used. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary time point, week 16, as well as at the other time points by time point-specific contrasts from the MMRM model.

For the binary efficacy endpoints, if rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used. If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal.

For the continuous efficacy endpoints, if a patient receives rescue medication, the data collected after rescue medication is initiated will be treated as missing.

Sensitivity analysis using other missing data handling approaches will also be performed.

Multiplicity Considerations

For US and US reference market submissions: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For the comparison of each dose regimen with placebo, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section of secondary endpoints.

For EMA and EMA reference market submissions: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both

co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section on section endpoints.

Safety Analysis: Will be based on the SAF. This includes TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and ECG results). A summary of safety results for each treatment group will be presented.

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Appendix 1: Factors to Consider in Assessing the Relationship of AEs to Study Drug

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibody
Anti-dsDNA	Anti-nuclear antibody against double-stranded DNA
Anti-TPO	Anti-thyroid peroxidase antibody
ARGUS	A Pharmacovigilance and Risk Management Safety Software System
AST	Aspartate Aminotransferase
BSA	Body surface area of involvement of atopic dermatitis
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full analysis set
GCP	Good Clinical Practice
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFNγ	Interferon gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin

IL-4Rα	Interleukin-4 receptor alpha
IRB	Institutional Review Board
ISR	Injection site reactions
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
NRS	Numerical rating scale
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PT	Preferred term
QOL	Quality of life
qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
TARC	Thymus and activation-regulated chemokine (CCL-17)
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (ie, itchiness), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD (Bieber 2008).

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction.

Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, hypothalamic pituitary axis effects, Cushing's disease, etc.). Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants (Schmitt 2007) and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation.

Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids (Schmitt 2009, Schram 2012, Akhavan 2008). Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

Up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents (Hart 2002, Wenzel 2007).

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. This population includes patients who are often treated with systemic corticosteroids, as well as other non-selective immunosuppressants, including cyclosporine, which are associated with significant toxicities. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. As of the cut-off date (28 March, 2014), there has been no evidence in the ongoing phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab for up to 12 weeks.

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 is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients 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). This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab.

1.2.2. Rationale for Dose Selection

The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). All patients randomized to receive treatment with dupilumab will get an initial loading dose of 600 mg on day 1. 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.

The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021), which evaluated dupilumab dose regimens of 300 mg qw, 300 mg q2w, 300 mg every 4 weeks (q4w), 200 mg q2w, and 100 mg q4w, versus placebo, administered for 16 weeks. An interim analysis was conducted after 240 patients completed 12 weeks of treatment. The interim analysis, which focused primarily on week 12 outcomes, indicated that dupilumab 100 mg q4w had suboptimal efficacy, whereas the 300 mg qw dupilumab regimen demonstrated the highest efficacy and was comparable to other dupilumab dosing regimens with respect to safety parameters. Therefore, the 300 mg qw dose was selected for further evaluation in phase 3 together with a 300 mg dose administered less frequently, q2w. Both doses were selected to be evaluated in this study to further refine the understanding of dose-response relationships in a larger sample of study patients and to explore a dose regimen with less frequent administration.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients 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 confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below).

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 at least 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 to receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by region (details will be specified in the interactive voice response system/interactive web response system [IVRS/IWRS] specifications document). Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks (Figure 1). Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Table 1 and Table 2).

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in a maintenance study. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

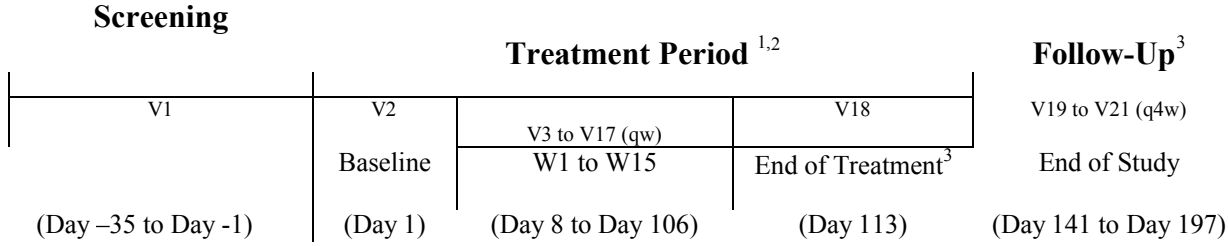
- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of

quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Patients with an ADA titer of ≥240 at their last study visit and some patients who are negative for ADA at their last study visit will be asked to return to the clinic to have additional ADA samples collected for analysis (see section 6.3.4.2 for details and time points).

Figure 1: Study Flow Diagram



[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered.

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

3.2. Planned Interim Analysis

No interim analysis is planned.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An independent data monitoring committee (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 is 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 600 patients will be enrolled at approximately 160 global sites.

4.2. Study Population

The study population consists of adults 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).

4.2.1. Inclusion Criteria

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

1. Male or female, 18 years or older
2. Chronic AD, (according to American Academy of Dermatology Consensus Criteria Eichenfield 2014), that has been present for at least 3 years before the screening visit
3. EASI score ≥16 at the screening and baseline visits
4. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits
5. ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits
6. Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks

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 (±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 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 re-screened after such documentation is obtained (ie, patients are shown to fail a 28-day course of mid-to-higher potency TCS [±TCI]).

7. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least 7 days before the baseline visit (NOTE: See exclusion criterion #6 for limitations regarding emollients)
8. Willing and able to comply with all clinic visits and study-related procedures
9. Able to understand and complete study-related questionnaires
10. Provide signed informed consent

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 an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
3. 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:
   - Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
   - Phototherapy for AD
4. Treatment with TCS or TCI within 1 week before the baseline visit
5. Treatment with biologics as follows:
   - Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte count returns to normal, whichever is longer
   - Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer
6. 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)
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit
8. Planned or anticipated use of any prohibited medications (see section 5.7.1) and procedures during study treatment
9. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit

10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: patients may be rescreened after infection resolves
11. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per investigator judgment
12. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
13. Positive with hepatitis B surface antigen (HBsAg) or hepatitis C antibody at the screening visit
14. At baseline, presence of any conditions listed as criteria for study drug discontinuation (see section 5.4.2)
15. Presence of skin comorbidities that may interfere with study assessments
16. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
17. 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
18. History of alcohol or drug abuse within 2 years of the screening visit
19. 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 (HbA1c $\geq$ 9%), patients with cardiovascular conditions (eg, stage 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 [CRFs], etc.)
20. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may 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, CRFs, etc.)

21. Planned or anticipated major surgical procedure during the patient's participation in this study
22. Patient is a member of the investigational team or his/her immediate family
23. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
24. Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 120 days after last dose of study drug. These include hormonal contraceptives, intrauterine device, or double barrier contraception (ie, condom + diaphragm) or a 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

    *For females, menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone level of ≥25 mU/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception

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 investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, adverse event (AE), treatment failure, protocol violation, cure, and for administrative, or other reasons. An excessive rate of withdrawals would diminish the informative value of the study data; therefore, unnecessary withdrawal of patients should be avoided. Patients who discontinue study treatment but who consent to remain in the study will continue to comply with study visits and assessments.

Patients who withdraw prematurely from the study will be asked to complete study assessments per section 6.2.5.

See section 3.1 for details of the maintenance and OLE studies.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

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

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

Patients will receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or weekly injections of matching placebo (following a placebo "loading dose") during the 16-week treatment period.

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 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 3 and 4 (weeks 1 and 2, respectively) and all other visits in the clinic. 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], 3 [day 8], and 4 [day 15]) and blood pressure and heart rate determined. The patient (or caregiver) will administer study drug outside of the clinic during weeks in which no clinic visit is scheduled.

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

The procedure for preparing the dupilumab dose for SC injection will be provided in the pharmacy manual. Subcutaneous injection sites 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 (ISRs), study drug should be administered only into areas of normal-looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual.

Detailed instructions for transport, storage, preparation, and administration of study drug will be provided by the site to the patient (or caregiver). Patients will complete a dosing diary to document compliance with self-injection of study drug outside the clinic.

5.2. Background Treatment

All patients are required to apply moisturizers at least twice daily for at least 7 days before randomization and to continue the treatment throughout the study (all 28 weeks where applicable). 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(s)

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. For the purpose of efficacy

analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication. All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

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 temporarily or 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 and complete all study assessments per the study schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per section 6.2.5.

5.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Evidence of pregnancy.
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status.
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks.
- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5 \times 10^3$ µL.

- Platelet count ≤50 x 10^3 µL.
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3x upper limit of normal (ULN) with total bilirubin >2x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome).
- Confirmed AST and/or ALT >5x 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).

- Other reasons that may lead to the permanent discontinuation of study treatment include:
  - Treatment with any prohibited concomitant medication or procedure (section 5.7.1).

5.4.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count ≤1.0 x 10^3/µL but >0.5 x 10^3/µL.
  - Platelet count ≤100 x 10^3/µL but >50 x 10^3/µL.
  - Creatine phosphokinase (CPK) >10x ULN.
- Other intercurrent illnesses or major surgery.

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 600 patients will be randomized on day 1 in a 1:1:1 ratio to receive qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo for 16 weeks. Patients will be randomized to a treatment group according to a central randomization scheme provided by an IVRS/IWRS to the designated site personnel or clinical staff members. Randomization will be stratified by disease severity (IGA 3 vs IGA 4) and

region (details will be specified in the IVRS/IWRS specifications document and will be documented in the clinical study report).

5.5.1. Blinding

With the exception of the statistician who provides the randomization sequence, the IDMC statistician, the IDMC members, and the provisions in section 5.5.2, this study will remain blinded to all individuals until the pre-specified 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 weekly injections of dupilumab or placebo starting at day 1. During weeks in which dupilumab is not administered in the q2w dosing regimen, patients will receive placebo.

Anti-drug antibody and drug concentration results will not be communicated to the sites, and the sponsor 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 the treatment assignment for a patient may be necessary due to a medical emergency, a serious adverse event (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). Details for emergency unblinding will be provided in the study manual.

- 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 at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2°C to 8°C 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

Any treatment administered from the time of informed consent 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 through week 16:

- Treatment with a live (attenuated) vaccine.
- Treatment with an investigational drug (other than dupilumab).
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

NOTE: If a patient receives treatment with systemic corticosteroids or other systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

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.

5.7.2.1. Cytochrome P450

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized.

However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (Abdel-Razzak 1993, Christensen 2012). Human peripheral blood mononuclear cells incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (Liptrott 2009).

Limited in vitro findings suggest that IL-4 and IL-13 may affect CYP levels and potentially activities. However, the clinical significance of these data is not fully understood. During the study treatment and at least up to the end of follow-up, investigators are cautioned to monitor clinical and laboratory signs that might indicate a potential drug-drug interaction in all patients receiving dupilumab concomitantly with narrow therapeutic index medications that are metabolized by CYP (see Investigator's Brochure for more details of such drugs). This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal, if needed.

For more details, refer to the study manual.

5.7.2.2. Prohibited Concomitant Medications or Procedures as Rescue

If medically necessary (eg, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator (see section 5.3 for details).

Blinded adjudication of concomitant medications may be performed to identify concomitant medications that confound study endpoints.

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 and Table 2.

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

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												
Safety:[7]														
Weight	X	X												
Height	X													
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)	**-35 to -1**	**D1**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)			**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV ab, HBsAg, Hep C Ab, TB[11]	X													
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[12]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[13]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

1 The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

2 For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

3 Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

4 Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

5 For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

6 Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

7 To be collected before the injection of study drug.

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

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

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

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs. A sub-study conducted at selected sites.

Table 2: Schedule of Events – (Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination)

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6,7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Total serum IgE				X	X	X	X	X	X
Antigen-specific IgE samples[11]				X			X	X	X
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[12]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[13]				X			X	X	X

[1] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

[2] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required

[3] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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

[4] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[5] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[6] To be collected before the injection of study drug.

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

[8] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

[11] Includes: antigen-specific IgE (region-specific allergen panels).

[12] Non-invasive skin swabs. A sub-study conducted at selected sites

[13] Patients with an ADA titer of ≥240 at the last study visit will be asked to return to the clinic to have additional samples collected for analysis (see section 6.3.4.2 for details and time points).

6.2. Study Visit Descriptions

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

1. Patient Reported Outcomes.
2. Investigator assessments (performed only by adequately trained investigators or sub-investigators; the same investigator or sub-investigator should perform all the evaluations for a given patient throughout the entire study period).
3. Safety and laboratory assessments.
4. Administration of study drug.

6.2.1. Visit 1/Screening/Day –35 to Day -1

After the patient has provided informed consent, the following information will be collected:

- Informed consent for optional assessments (for patients who consent to participate in the genomic sub-study)
- Inclusion/exclusion
- Medical history and concurrent illnesses
- Demographics
- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Training on IVRS
- Pruritus Numerical Rating Scale (NRS)
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - Patient Oriented Eczema Measure (POEM)
  - Hospital Anxiety and Depression Scale (HADS)
  - Dermatology Life Quality Index (DLQI)
  - European Quality of Life-5 Dimensions (EQ-5D)
  - Asthma Control Questionnaire (ACQ-5)
  - Sinonasal Outcome Test (SNOT-22)
- Patient Global Assessment of Disease
- Vital signs
- Investigator's Global Assessment (IGA)

- Eczema Area and Severity Index (EASI)
- Global Individual Signs Score (GISS)
- SCORing Atopic Dermatitis (SCORAD)
- Body Surface Area of (BSA) involvement of atopic dermatitis
- Weight
- Height
- Physical examination
- Electrocardiogram (ECG)
- Laboratory testing:
  - HIV ab
  - HBsAg
  - Hepatitis C antibody
  - TB testing (on a country-by-country basis)
  - Hematology and Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - Thymus activation-regulated chemokine (TARC)
  - Total serum IgE
  - Antigen-specific IgE (region-specific allergen panels)
  - Highly sensitive C-reactive protein (hs-CRP)
  - Anti-nuclear antibody (ANA)
  - Anti-double-stranded DNA (anti-dsDNA)
  - Anti-thyroid peroxidase (anti-TPO)
  - Skin microbiome samples (select sites)
  - Research samples

6.2.2. Treatment Period

6.2.2.1. Visit 2/Baseline/Day 1

The following information will be collected:

- Inclusion/Exclusion
- Concomitant medications

- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology and Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA

  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - DNA and RNA samples
  - Functional dupilumab pharmacokinetic (PK) sample
  - Anti-dupilumab antibody sample
- Randomization
- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.2. Visit 3/Week 1/Day 8 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA

- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.3. Visit 4/Week2/Day 15 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample

- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection
- Provide patient dosing diary
- Study drug dispensation

6.2.2.4. Visit 5/Week 3/Day 22 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.5. Visit 6/Week 4/Day 29 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment

- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.6. Visit 7/Week 5/Day 36 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.7. Visit 8/ Week 6/Day 43 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.8. Visit 9/Week 7/Day 50 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS

- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.9. Visit 10/ Week 8/Day 57 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE

  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.10. Visit 11/Week 9/Day 64 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.11. Visit 12/Week 10/Day 71 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug.
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.12. Visit 13/Week 11/Day 78 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.13. Visit 14/Week 12/Day 85 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD

- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.14. Visit 15/Week 13/Day 92 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.15. Visit 16/Week 14/Day 99 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administer study drug.
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.16. Visit 17/Week 15/Day 106 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.17. Visit 18/End of Treatment/Week 16/Day 113 (±3 days)

The end of treatment at week 16 (visit 18) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment

- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.3. Follow-up Period

6.2.3.1. Visit 19/Week 20/Day 141 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.3.2. Visit 20/Week 24/Day 169 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.4. Visit 21/End of Study Visit/Week 28/Day 197 (±3 days)

The end of study at week 28 (visit 21) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:

  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient global assessment of disease
- Patient global assessment of treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)

- Research samples
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

6.2.5. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 16) will be asked to return to the clinic for 2 visits: once for early termination assessments, and again at week 16 (primary endpoint visit), as described in section 6.2.2.17. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA

- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.6. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. During an unscheduled visit, any of the procedures noted may be performed, but not all are required.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)

- Research samples
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

Assessments performed only at the screening and/or baseline visit include: medical history, medication history, demographics, diagnosis of chronic AD, HBsAg, anti-HIV antibody, and hepatitis C antibody. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

6.3.2. 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 will be administered only to the subset of patients who fluently speak a language in which the assessment tool has been translated. These 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 POEM, HADS, DLQI, and EQ-5D).

6.3.2.1. Patient Assessment of Pruritus

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average 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 overall (on average) during the previous 24 hours?"
- 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.2. Patient-Assessed Pruritus Categorical Scale

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in 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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.3. 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 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 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 6.2.

The POEM is provided in the study reference manual.

6.3.2.4. 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 6.2.

The HADS is provided in the study reference manual.

6.3.2.5. Patient-Reported Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL (Badia 1999). The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. 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 6.2.

The DLQI is provided in the study reference manual.

6.3.2.6. Patient-Assessed EQ-5D

The EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement (ie, no problems, some problems, or severe problems) in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

The EQVAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)". This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

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 6.2.

The EQ-5D is provided in the study reference manual.

6.3.2.7. Patient Global Assessment of Disease

Patients will rate their overall wellbeing based on a 5-point Likert scale from poor to excellent. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent." Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.8. Patient Global Assessment of Treatment

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent". Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.9. Juniper Asthma Control Questionnaire

The 5-question version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.10. Sinonasal Outcome Test

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.11. Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.12. 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 6.2.

The IGA is provided in the study reference manual.

6.3.2.13. 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 6.2.

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

6.3.2.14. Body Surface Area Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 6.2.

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

6.3.2.15. 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. The GISS will be assessed at time points according to section 6.2.

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

6.3.2.16. SCORing Atopic Dermatitis

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). There are 3 components to the assessment: A = extent or affected body surface area, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see section 6.3.2.14) 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, 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 VAS, 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 6.2.

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

6.3.2.17. 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 (pre-dose). Subsequent photographs of the same area will be taken at week 16 (end of treatment) and week 28 (end of study).

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

6.3.3. Safety Procedures

6.3.3.1. Physical Examination

A thorough and complete physical examination will be performed at time points according to section 6.2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

6.3.3.2. Weight and Height

Weight and height will be determined at time points according to section 6.2.

6.3.3.3. Vital Signs

Vital signs, including heart rate, blood pressure, body temperature, and respiration rate, will be collected pre-dose at time points according to section 6.2. Vital signs (blood pressure and heart rate) will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation.

6.3.3.4. Electrocardiogram

Electrocardiograms will be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to section 6.2. The ECG strips or reports will be retained with the source documentation, and the results will be documented in the electronic case report form.

Electrocardiogram results will be interpreted by a central reading center. Instructions for performing the assessment and transmitting ECG data are provided in the study reference manual.

6.3.3.5. Laboratory Testing

Hematology, chemistry, urinalysis, and serum pregnancy testing samples will be analyzed by a central laboratory. The urine pregnancy test kit will be provided to the site by the laboratory.

Blood samples for serum chemistry and hematology testing will be collected to measure overall patient health at screening. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. 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 6.2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK

Hematology

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

Urinalysis

Microscopic analysis will only be done in the event of abnormal dipstick results.

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

Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at time points according to section 6.2.

Testing for HIV antibody, HBsAg, and hepatitis C antibody will be performed at screening. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

Abnormal Laboratory Values and Laboratory Adverse Events

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

- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in section 7.2.5.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Samples for dupilumab concentration will be collected at time points listed in section 6.2.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in section 6.2.

Patients with an ADA titer of ≥240 at their last study visit (early termination or end of study) will be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months, until their titers fall below 240. Some patients who are negative for ADA at their last study visit will also be asked to return to the clinic within 6 to 12 months from their last dose of study drug to have additional ADA samples collected to maintain the blind.

6.3.5. Research Testing

Research assessments are performed for exploratory purposes only; results for assessments in the sub-sections below will not be reported in the clinical study report. Results will be reported separately from the clinical study report.

6.3.5.1. Research Samples

Research samples (serum/plasma) will be collected at time points according to section 6.2.

Use and Storage of Research Samples (Serum/Plasma)

Research serum and plasma samples will be collected to study the effects of the study drug on modulation of the IL-4 receptor as well as on atopic disease processes. Unused samples collected for drug concentration or ADA analyses may also be used for other research purposes. Remaining samples may be stored (up to 10 years) for future use in experiments related to AD or related diseases. If necessary, the samples may also be used to identify markers associated with toxicity.

6.3.5.2. Genomics Sub-Study - Optional

Patients will be asked to participate in an optional genomics sub-study. Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study informed consent form (ICF) before collection of the samples. Blood for DNA extraction should be collected on day 1/baseline (pre-dose), but may be collected at any study visit. RNA samples will be collected at time points according to section 6.2. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA and RNA samples for the genomics sub-study will be double-coded as defined by the ICH guideline E15. Sub-study samples may be stored for up to 10 years after the final date of the clinical study report and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to IL-4/13 pathway inhibition (via IL-4Rα blockade), atopic disease risk, prognosis and progression, or other clinical outcome measures. These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Genome-wide studies, including (but not limited to) single nucleotide polymorphism analyses and genomic sequencing may also be performed. If indicated, genomic analyses may also be performed to identify markers associated with toxicity.

6.3.5.3. Exploratory Biomarker Testing

Biomarkers to be analyzed in this study are: TARC, total serum IgE, antigen-specific IgE (region-specific, allergen-specific panels), *S. aureus* enterotoxin A-specific IgE, *S. aureus* enterotoxin B-specific IgE, hs-CRP, ANA, anti dsDNA, anti-TPO. Skin swab samples for skin microbiome testing will be banked. Samples will be collected at time points according to section 6.2. These are exploratory assessments to further the understanding of AD-associated biomarkers and the response to dupilumab treatment. The results of these tests will not be used to evaluate patient eligibility for study participation.

Thymus and activation regulated chemokine and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug. These results may also 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, and will be evaluated as an exploratory marker of efficacy. These markers may also be assessed for their potential value in predicting treatment response.

Staphylococcus aureus colonization and infection on the skin is a significant complication for many AD patients. To determine whether or not dupilumab treatment can reduce colonization and/or infection, exploratory samples for skin microbiome analyses will be banked. Non-invasive skin swab samples from lesional and non-lesional skin will be collected to characterize the skin microbiome diversity and *S. aureus* abundance. Skin swab samples for culturing (eg, semi-quantitative analysis of methicillin-sensitive and methicillin-resistant *S. aureus* colonization) may also be collected.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs 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 also be tested for predictive utility.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti dsDNA, anti-TPO, and ANA) will be measured.

Detailed instructions for sample collection are provided in the laboratory manual.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

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

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

7.1.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as 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).

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 16 weeks 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 in this study include:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Severe ISRs that last longer than 24 hours
- Mycosis fungoides or other forms of cutaneous T cell lymphoma
- Any severe infection; any infection requiring treatment with parenteral antibiotics/anti-viral/anti-fungal agent; any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks; any clinical endoparasitosis; any opportunistic infection

Note: Generally, all uncommon, atypical, peculiar, or unusually persistent infections, especially viral infections, should be reported as AESIs.

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.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

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

Is there a reasonable possibility that the adverse event was 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

A list of factors to consider in assessing the relationship of AES to study, see Appendix 1.

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, AD history and characteristics, and medication history.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoint

During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries. As a result:

The primary endpoint is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Medicines Agency (EMA) and EMA Reference Market Countries only, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

8.2.2. Secondary Endpoints

The secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16

- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in HADS
- Change from baseline to week 16 in POEM
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of skin infection treatment-emergent adverse events (TEAE) requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

8.2.3. Other Endpoints and Assessments

- Absolute and percent change from baseline to week 16 in: EQ-5D, Patient Global Assessment of Disease and Patient Global Assessment of Treatment
- Distribution of disease severity scores (eg, IGA, EASI, SCORAD) and their change from baseline
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Changes in efficacy parameters through week 16
- Characterization of dupilumab serum concentrations through week 16
- Correlation analyses:
  - Body weight vs serum concentrations
  - Serum concentrations vs clinical outcomes
  - Body weight vs clinical outcomes
  - Association between baseline biomarkers (eg, TARC, total IgE) and clinical response

- Incidence of dupilumab ADA

8.3. Pharmacokinetic Variables

The PK variables may include, but are not limited to, the following:

- C_{trough} over time
- C_{last}
- T_{last}
- Time to steady state
- $C_{troughSS}$ - steady state trough concentration

8.4. Anti-drug Antibody Variables

ADA variables include status (positive or negative) and titer as follows:

- Total positive at any time
- Pre-existing immunoreactivity - a positive ADA response at baseline
- Treatment emergent - defined as either any positive response when baseline results are negative, or if any post treatment ADA response is ≥4-fold over baseline titer levels
- Persistently positive
- Transiently positive
- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

If a sample tests positive for ADA, the neutralizing activity of the ADA will be assessed.

9. STATISTICAL PLAN

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

Analysis variables are listed in section 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

Disease severity and region 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

To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo.

9.3. Analysis Sets

9.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients who receive any study medication. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

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). If a patient receives a dose regimen different to that assigned during the study, this patient will be considered as treated by the lowest active dose regimen. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

9.3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all randomized patients with at least 1 post-baseline drug concentration result.

9.3.4. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all randomized patients with at least 1 post-baseline ADA result.

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, median, standard deviation, 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. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

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 (region, disease severity) will be used for the percentage of patients with IGA 0 or 1 at week 16 or percentage of patients with EASI-75 at week 16.

To account for the impact of rescue medication on the efficacy effect:

For the binary efficacy endpoints, if rescue medication is used (see section 5.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.

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

Sensitivity analysis using 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.

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, a mixed-effect model with repeated measures (MMRM) will be used, which will account for the missing data. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. The MMRM model will provide baseline adjusted least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p-values for treatment comparisons by the appropriate time point-specific contrasts from the model. Additional details on the MMRM model will be provided in the SAP.

To account for the impact of rescue medication on the efficacy effect:

Continuous efficacy endpoints: if a patient receives rescue medication that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue medication is initiated will be treated as missing.

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

In addition to the MMRM model, sensitivity analysis using LOCF and/or the multiple imputation (MI) methods followed by an analysis of covariance model will be conducted. Robustness of the MMRM model to departure from the missing-at-random assumption will be explored using sensitivity analysis based on the pattern mixture model plus MI approach. Additional details on these sensitivity analyses will be provided in the SAP.

9.5.2.3. Multiplicity Considerations

For US and US Reference Market Countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

For EMA and EMA reference market submissions:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary

endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients achieving EASI-75 (≥75% reduction from baseline in EASI score at week 16 (this is not a secondary endpoint for the EMA as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in HADS
- Change from baseline to week 16 in POEM
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16
- Incidence of TESAEs from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

9.5.3. Safety Analysis

Safety analysis will be based on the SAF. This includes reported TEAEs and other safety information (ie, 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 pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug (day 1) to the end of the study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing 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 patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

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

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

9.5.3.2. Other Safety

Vital Signs

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

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.

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

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for 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 and calculated as:

(Date of last study drug injection – date of first study drug injection) + 7 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:

Treatment Compliance =

(Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) x 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

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

9.5.5. Analysis of Anti-Drug Antibody Data

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

9.5.6. Analysis of Quality of Life Data

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

9.5.7. 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-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 non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

The CRF data for this study will be collected with an electronic data capture 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, study drug supply
- EDC system – data capture/uploading and storing photographs
- Statistical Analysis Software (SAS) – statistical review and analysis
- ARGUS – a PVRM Safety System
- nQuery Advisor – sample size calculations

11. STUDY MONITORING

11.1. Monitoring of Study Sites

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

11.2. Source Document Requirements

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

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

11.3. Case Report Form Requirements

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

study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

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

12. AUDITS AND INSPECTIONS

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

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

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

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

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) must be kept in strict confidence.

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

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

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS dated 08 AUG 2014, and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

Appendix 1: Factors to Consider in Assessing the Relationship of AEs to Study Drug

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

No:

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

Yes:

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

NOTE: This list is not exhaustive.

Clinical Study Protocol

A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Compound:	Dupilumab
Study Name:	Liberty AD SOLO 1
Clinical Phase:	3
Protocol Number:	R668-AD-1334
Protocol Version:	R668-AD-1334.02 JP
Amendment 2 Date of Issue:	05 FEB 2015
Amendment 1 Date of Issue:	10 NOV 2014
Original Date of Issue:	08 AUG 2014
Scientific/Medical Monitor:	Marius Ardeleanu, MD Senior Director, Clinical Sciences Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

Confidential: This document contains confidential information that is the property of Regeneron Pharmaceuticals, Inc., and must not be disclosed to anyone other than designees of Regeneron for the conduct of the study, the recipient clinical Investigator(s) and their designees and members of the Institutional Review Board. This information must not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Regeneron Pharmaceuticals, Inc.

AMENDMENT 2 (05 FEB 2015)

The purposes of amendment 2 are to:

- Add text to indicate that for background treatment with moisturizers (emollients), to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit
- Separate the secondary endpoints into 2 parts: Key Secondary Endpoints and Other Secondary Endpoints
- Rearrange "other secondary endpoints": move up "change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)" to be above the endpoint "change from baseline to week 16 in Hospital Anxiety Depression Scale (HADS)"
- Revise the following endpoints in the "other secondary endpoints" section: from "change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)" to "percent change from baseline to week 16 in SCORAD"; from "change from baseline to week 16 in Global Individual Signs Score (GISS) (erythema, infiltration/population, excoriations, lichenification)" to "percent change from baseline to week 16 in GISS (erythema, infiltration/population, excoriations, lichenification)"
- Move the following secondary endpoint to the end of "other secondary endpoints": "incidence of skin infection treatment-emergent adverse events (TEAEs) requiring systemic treatment from baseline through week 16"
- Revise the definition for the full analysis set (FAS) from "the FAS includes all randomized patients who receive any study medication" to "the FAS includes all randomized patients", and add per protocol set (PPS) for efficacy analysis
- Add description of methods for missing data imputation (multiple imputation [MI] Statistical Analysis Software [SAS] procedure with Markov Monte Carlo algorithm) and data analysis (analysis of covariance [ANCOVA] and the SAS MIANALYZE procedure) for continuous secondary endpoints to be used in US and US reference market countries, and revise text relevant to this topic
- Add an inclusion criterion requiring a patient to have a baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥3 to be eligible to enroll in the study
- Add a note in exclusion criterion #11 to emphasize that patients with confirmed or suspected active or untreated latent tuberculosis (TB) are not eligible for this study
- Revise footnote 13 of Table 1 and footnote 12 of Table 2 to clarify that non-invasive skin swabs is a sub-study that may be (instead of "will be", as previously stated) conducted at selected sites

- Clarify that instructions for performing the assessment and transmitting electrocardiogram (ECG) data are provided in the central ECG reference manual, instead of the study reference manual (as previously stated)
- Add the following as a potential use of research samples: to study biomarkers that may have predictive utility for response to dupilumab treatment
- For exploratory biomarker testing, change the phrase from "… samples … will be banked" to "… samples … may be banked"
- Revise the language for the endpoint "changes in efficacy parameters through week 16" in the "other endpoints and assessments" section to include absolute and percent changes in efficacy parameters through week 16
- Add description for a sensitivity analysis for binary endpoints
- Make editorial changes for clarity and/or consistency

The following table outlines the changes made to protocol R668-AD-1334.02JP and the affected sections:

Change	**Section Changed**
Add text to indicate that for background treatment with moisturizers (emollients), to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit	Synopsis: Study Design Section 3.1 Study Description and Duration Section 4.2.1 Inclusion Criteria - Inclusion Criterion #8 Section 5.2 Background Treatment
Separate the secondary endpoints into 2 parts: Key Secondary Endpoints and Other Secondary Endpoints	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints
Rearrange "other secondary endpoints": move up "change from baseline to week 16 in POEM" to be above the endpoint "change from baseline to week 16 in HADS"	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints Section 9.5.2.3 Multiplicity Considerations
Revise the following endpoints in the "other secondary endpoints" section: from "change from baseline to week 16 in SCORAD" to "percent change from baseline to week 16 in SCORAD"; from "change from baseline to week 16 in GISS (erythema, infiltration/population, excoriations, lichenification)" to "percent change from baseline to week 16 in GISS (erythema, infiltration/population, excoriations, lichenification)"	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints Section 9.5.2.3 Multiplicity Considerations
Move the following endpoint to the end of "other secondary endpoints": "incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16"	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints Section 9.5.2.3 Multiplicity Considerations

Revise the definition for the FAS from "the FAS includes all randomized patients who receive any study medication" to "the FAS includes all randomized patients" and add PPS for the efficacy analysis	Synopsis: Statistical Plan Section 9.3.1 Efficacy Analysis Sets
Add description of methods for missing data imputation (MI SAS procedure with Markov Monte Carlo algorithm) and data analysis (analysis of covariance [ANCOVA] and the SAS MIANALYZE procedure) for continuous secondary endpoints to be used in US and US reference market countries, and revise text relevant to this topic	Synopsis: Statistical Plan Section 9.5.2.2 Secondary Efficacy Analysis
Add an inclusion criterion requiring a patient to have a baseline Pruritus NRS average score for maximum itch intensity ≥3 to be eligible to enroll in the study	Section 4.2.1 Inclusion Criteria - Inclusion Criterion #6 (added)
Add a note in exclusion criterion #11 to emphasize that patients with confirmed or suspected active or untreated latent tuberculosis (TB) are not eligible for this study	Section 4.2.2 Exclusion Criteria – Exclusion Criterion #11
Revise footnote 13 of Table 1 and footnote 12 of Table 2 to clarify that non-invasive skin swabs is a sub-study that may be (instead of "will be", as previously stated) conducted at selected sites	Table 1 Schedule of Events (Screening, Baseline, and Treatment Period) - footnote 13 Table 2, - (Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination) - footnote 12 Section 6.3.5.3 Exploratory Biomarker Testing
Clarify that instructions for performing the assessment and transmitting ECG data are provided in the central ECG reference manual, instead of the study reference manual (as previously stated)	Section 6.3.3.5 Electrocardiogram
Add the following as a potential use of research samples: to study biomarkers that may have predictive utility for response to dupilumab treatment	Section 6.3.5.1 Research Samples
For exploratory biomarker testing, change the phrase from "… samples … will be banked" to "… samples … may be banked"	Section 6.3.5.3 Exploratory Biomarker Testing
Revise the language for the endpoint "changes in efficacy parameters through week 16" in the "other endpoints and assessments" section to include "absolute and percent changes in efficacy parameters through week 16"	Section 8.2.3 Other Endpoints and Assessments

Add description for a sensitivity analysis for binary endpoints	Section 9.5.2.1 Primary Efficacy Analysis
Editorial changes for clarity and/or consistency	Amendment 1 Summary Synopsis: Endpoints, Statistical Plan List of Abbreviations and Definitions of Terms Section 5.2 Background Treatment Table 1 Schedule of Events (Screening, Baseline, and Treatment Period), row for HIV Ab Section 6.2.1 Visit 1/Screening/Day –35 to Day -1 Section 8.2.1 Primary Endpoint Section 8.2.2 Secondary Endpoints Section 9.5.2.2 Secondary Efficacy Analysis Section 9.5.2.3 Multiplicity Considerations

AMENDMENT 1 (10 NOV 2014)

The purposes of this Japan-specific amendment 1 are to incorporate changes made to the global amendment 1 and to make Japan-specific changes; the combined changes include the following:

- Update emollient use
- Clarify exclusion criterion #7
- Add positive hepatitis B core antibody (HBcAb) as an exclusion
- Make Japan-specific changes in response to Japanese Health Authority requests
- Clarify rescue treatment
- Modify section on discontinuation of study drug
- Change the time period for prohibition of listed medications from “through week 16” to “during the study”
- Add immunomodulating biologics to the list of prohibited medications
- Modify frequency of patient self-assessment for pruritus
- Specify that fasting is recommended prior to collecting blood samples for laboratory testing
- Add provision for additional tests when total bilirubin is > upper limit of normal (ULN) and creatine phosphokinase (CPK) is >5X ULN
- Make minor edits

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis
Site Location(s)	Global
Principal Investigator	Not Applicable
Objective(s)	The primary objective is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe atopic dermatitis (AD). The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD.
Study Design	This is a randomized, double-blind, placebo-controlled, parallel group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28-weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below). After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 (emollients) twice daily for at least the 7 consecutive days immediately 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 non-lesional skin designated for such assessments for at least 8 hours before each clinic visit. Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio to receive once weekly (qw) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, every 2 weeks (q2w) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) = 3] vs. severe [IGA = 4] AD) and by region. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits. The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoints will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not been rescued will be eligible to participate in a maintenance study. Patients who meet these criteria but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 to 4 (whichever comes first).

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Safety, laboratory, and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events.

Study Duration	Each patient's participation in the study will be up to approximately 21 weeks or 33 weeks, including the screening period.
Population	
Sample Size:	Approximately 600 patients will be enrolled at approximately 160 global study sites
Target Population:	The study population includes adults 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)
Treatment(s)	
Study Drug	Dupilumab SC
Dose/Route/Schedule:	Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg dupilumab in a 2 mL volume) on day 1 followed by 300 mg in 2 mL qw from week 1 through week 15 Or Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg in a 2 mL volume) on day 1 followed by 300 mg in 2 mL q2w from week 1 through week 15. The last dose of study drug for both regimens will be at week 15.
Placebo Route/Schedule:	Matching placebo SC injection. Loading dose for the placebo arm consists of 2 injections, each containing placebo formulation in a 2 mL volume, administered at day 1 and followed by qw injections of 2 mL placebo formulation from week 1 through week 15 (last dose of study drug will be at week 15).
Endpoint(s)	During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries.
Primary:	• Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
Co-Primary for European Union (EU) and EU Reference Market Countries, and Japan:	• Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 • Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

Secondary:	**Key Secondary Endpoints:** • Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EU and EU reference market countries, and Japan as it is already a co-primary endpoint) • Percent change from baseline to week 16 in Pruritus Numerical Rating Scale (NRS) • Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16 **Other Secondary Endpoints:** • Percent change in EASI score from baseline to week 16 • Change from baseline to week 16 in percent Body Surface Area (BSA) • Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD) • Percent change from baseline to week 16 in Global Individual Signs Score (GISS) (erythema, infiltration/population, excoriations, lichenification) • Change from baseline to week 16 in Dermatology Life Quality Index (DLQI) • Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM) • Change from baseline to week 16 in Hospital Anxiety Depression Scale (HADS) • Percent change from baseline to week 2 in pruritus NRS • Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16 • Incidence of treatment-emergent adverse events (TEAEs) leading to treatment discontinuation from baseline through week 16 • Overall incidence of TEAEs through week 16 • Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
Procedures and Assessments	A variety of parameters will be collected during the study to assess the efficacy of dupilumab, including measures of AD severity, and patient-reported measures of AD symptoms and quality of life (QOL). The safety of dupilumab in this population will be assessed by evaluating TEAEs, detailed medical history, thorough physical examination, vital signs,

	electrocardiograms (ECGs), and clinical laboratory testing. Concomitant medications and procedures will be collected from time of informed consent to the end of the study. Safety data will be reviewed on an ongoing basis by the sponsor. An independent data monitoring committee (IDMC) that oversees the entire dupilumab clinical development program will review safety data periodically in an unblinded fashion and will advise the sponsor of potential safety signals. Blood samples will be collected for dupilumab concentration and anti-dupilumab antibody (ADA) levels at pre-determined time points. Research samples and samples for exploratory biomarker analysis will be collected.
Statistical Plan	**Sample Size:** To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total with a randomization ratio of 1:1:1 dupilumab, 300 mg qw: 300 mg q2w: placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment) to detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively. The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively. The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. **Efficacy Analysis Set:** The full analysis set (FAS) includes all randomized patients. Efficacy analysis will be based on treatment allocated at randomization (as randomized), which will be stratified by disease severity and region. The per protocol set (PPS) includes all patient 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. The criteria of major protocol deviations are defined as the

following:

- A patient who does not receive treatment as randomized
- Any major violations of efficacy-related entry criteria
- The percentage of a patient's compliance with study drug injection is <80% or >120% of the scheduled doses during the study treatment period

Methods:

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

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

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.

Primary Efficacy Analysis

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

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, different analysis methods will be used:

- For US and US reference market countries: Missing data from the randomized population will be imputed multiple times to generate a complete dataset at each imputation by using the multiple imputation (MI) Statistical Analysis Software (SAS) procedure with Markov Monte Carlo algorithm. These complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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.
- For EU and EU reference market countries, and Japan: A mixed-effect model with repeated measures (MMRM) will be used. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary time

point, week 16, as well as at the other time points by time point-specific contrasts from the MMRM model.

For the binary efficacy endpoints, if rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used. If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal.

For the continuous efficacy endpoints, if a patient receives rescue medication, the data collected after rescue medication is initiated will be treated as missing.

Sensitivity analysis using other missing data handling approaches will also be performed.

Multiplicity Considerations

For US and US reference market countries: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For the comparison of each dose regimen with placebo, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section of secondary endpoints.

For EU and EU reference market countries, and Japan: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section on section endpoints.

Safety Analysis: Will be based on the SAF. This includes TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and ECG results). A summary of safety results for each treatment group will be presented.

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Appendix 1. Factors to Consider in Assessing the Relationship of AEs to Study Drug

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of covariance
Anti-dsDNA	Anti-nuclear antibody against double-stranded DNA
Anti-TPO	Anti-thyroid peroxidase antibody
ARGUS	A Pharmacovigilance and Risk Management Safety Software System
AST	Aspartate Aminotransferase
BSA	Body surface area of involvement of atopic dermatitis
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EU	European Union
FAS	Full analysis set
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
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFNγ	Interferon gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E

IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
IRB	Institutional Review Board
ISR	Injection site reactions
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
NRS	Numerical Rating Scale
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term
QOL	Quality of life
qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
TARC	Thymus and activation-regulated chemokine (CCL-17)
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (ie, itchiness), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD (Bieber 2008).

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction.

Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, hypothalamic pituitary axis effects, Cushing's disease, etc.). Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants (Schmitt 2007) and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation.

Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids (Schmitt 2009, Schram 2012, Akhavan 2008). Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

Up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents (Hart 2002, Wenzel 2007).

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. This population includes patients who are often treated with systemic corticosteroids, as well as other non-selective immunosuppressants, including cyclosporine, which are associated with significant toxicities. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. As of the cut-off date (28 March, 2014), there has been no evidence in the ongoing phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab for up to 12 weeks.

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 is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients 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). This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab.

1.2.2. Rationale for Dose Selection

The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). All patients randomized to receive treatment with dupilumab will get an initial loading dose of 600 mg on day 1. 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.

The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021), which evaluated dupilumab dose regimens of 300 mg qw, 300 mg q2w, 300 mg every 4 weeks (q4w), 200 mg q2w, and 100 mg q4w, versus placebo, administered for 16 weeks. An interim analysis was conducted after 240 patients completed 12 weeks of treatment. The interim analysis, which focused primarily on week 12 outcomes, indicated that dupilumab 100 mg q4w had suboptimal efficacy, whereas the 300 mg qw dupilumab regimen demonstrated the highest efficacy and was comparable to other dupilumab dosing regimens with respect to safety parameters. Therefore, the 300 mg qw dose was selected for further evaluation in phase 3 together with a 300 mg dose administered less frequently, q2w. Both doses were selected to be evaluated in this study to further refine the understanding of dose-response relationships in a larger sample of study patients and to explore a dose regimen with less frequent administration.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients 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 confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below).

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 (emollients) at least twice daily for at least the 7 consecutive days immediately 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 non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio to receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by region (details will be specified in the interactive voice response system/interactive web response system [IVRS/IWRS] specifications document). Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks (Figure 1). Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Table 1 and Table 2).

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

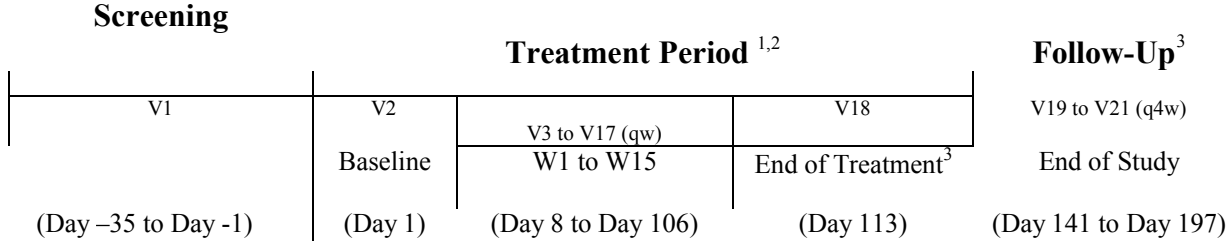
Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in a maintenance study. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Patients with an ADA titer of ≥240 at their last study visit and some patients who are negative for ADA at their last study visit will be asked to return to the clinic to have additional ADA samples collected for analysis (see section 6.3.4.2 for details and time points).

Figure 1: Study Flow Diagram



[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered.

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

3.2. Planned Interim Analysis

No interim analysis is planned.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An independent data monitoring committee (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 is 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 600 patients will be enrolled at approximately 160 global sites.

4.2. Study Population

The study population consists of adults 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).

4.2.1. Inclusion Criteria

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

1. Male or female, 18 years or older
2. Chronic AD, (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]), that has been present for at least 3 years before the screening visit
3. EASI score ≥16 at the screening and baseline visits
4. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits
5. ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits
6. Baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥3

   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. Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks

   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 (±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 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 re-screened after such documentation is obtained (ie, patients are shown to fail a 28-day course of mid-to-higher potency TCS [±TCI]).

8. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (NOTE: See exclusion criterion #6 for limitations regarding emollients). (See background treatment with topical emollient in section 5.2.)
9. Willing and able to comply with all clinic visits and study-related procedures
10. Able to understand and complete study-related questionnaires
11. Provide signed informed consent

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 an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
3. 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:
   - Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
   - Phototherapy for AD
4. Treatment with TCS or TCI within 1 week before the baseline visit
5. Treatment with biologics as follows:
   - Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte count returns to normal, whichever is longer

- Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer

6. 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)
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit
8. Planned or anticipated use of any prohibited medications (see section 5.7.1) and procedures during study treatment
9. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: patients may be rescreened after infection resolves
11. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment
    NOTE: Suspected active or untreated latent TB will be based on medical history, physical examination, or screening chest X-ray. Patients with confirmed or suspected active or untreated latent TB are not eligible for this study.
12. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
13. Positive with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at the screening visit
    NOTE: Patients who are HBsAg negative and HBsAb positive are considered immune after a natural infection has cleared or they have been vaccinated against hepatitis B. Therefore, they are acceptable for the study. These patients will be allowed to enroll into the study, but will be followed using routine clinical and liver function tests, as well as hepatitis B viral load testing at screening, and periodically during study treatment.
14. At baseline, presence of any conditions listed as criteria for study drug discontinuation (see section 5.4.2)
15. Presence of skin comorbidities that may interfere with study assessments
16. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
17. 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

18. History of alcohol or drug abuse within 2 years of the screening visit
19. 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 (HbA1c ≥ 9%), patients with cardiovascular conditions (eg, stage 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 [CRFs], etc.)
20. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may 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, CRFs, etc.)
21. Planned or anticipated major surgical procedure during the patient's participation in this study
22. Patient is a member of the investigational team or his/her immediate family
23. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
24. Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 120 days after last dose of study drug. These include hormonal contraceptives, intrauterine device, or double barrier contraception (ie, condom + diaphragm) or a 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

    *For females, menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone level of ≥25 mU/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception.

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 investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, adverse event (AE), treatment failure, protocol violation, cure, and for administrative, or other reasons. An excessive rate of withdrawals would diminish the informative value of the study data; therefore, unnecessary withdrawal of patients should be avoided. Patients who discontinue study treatment but who consent to remain in the study will continue to comply with study visits and assessments.

Patients who withdraw prematurely from the study will be asked to complete study assessments per section 6.2.5.

See section 3.1 for details of the maintenance and OLE studies.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

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

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

Patients will receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or weekly injections of matching placebo (following a placebo "loading dose") during the 16-week treatment period.

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 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 3 and 4 (weeks 1 and 2, respectively) and all other visits in the clinic. 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], 3 [day 8], and 4 [day 15]) and blood pressure and heart rate determined. The patient (or caregiver) will administer study drug outside of the clinic during weeks in which no clinic visit is scheduled.

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

The procedure for preparing the dupilumab dose for SC injection will be provided in the pharmacy manual. Subcutaneous injection sites 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 (ISRs), study drug should be administered only into areas of normal-looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual.

Detailed instructions for transport, storage, preparation, and administration of study drug will be provided by the site to the patient (or caregiver). Patients will complete a dosing diary to document compliance with self-injection of study drug outside 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 and to continue 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 non-lesional 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.

5.3. Rescue Treatment(s)

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. For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication. All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

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 temporarily or 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 and complete all study assessments per the study schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per section 6.2.5.

5.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Evidence of pregnancy
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3x upper limit of normal (ULN) with total bilirubin >2x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5x 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).
- Other reasons that may lead to the permanent discontinuation of study treatment include:
  - Treatment with any prohibited concomitant medication or procedure (section 5.7.1)

5.4.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.0 \times 10^3/\mu L$ but $>0.5 \times 10^3/\mu L$
  - Platelet count $\leq 100 \times 10^3/\mu L$ but $>50 \times 10^3/\mu L$
  - Creatine phosphokinase (CPK) >10x ULN
- Other intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (eg, cyclosporine, methotrexate, azathioprine, mycophenalate-mofetil, Janus kinase inhibitors, biologic agents, etc)

After the lab abnormality leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. Similarly, study treatment may resume after the medication leading to suspension of dosing is discontinued. 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 600 patients will be randomized on day 1 in a 1:1:1 ratio to receive qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo for 16 weeks. Patients will be randomized to a treatment group according to a central randomization scheme provided by an IVRS/IWRS to the designated site personnel or clinical staff members. Randomization will be stratified by disease severity (IGA 3 vs IGA 4) and region (details will be specified in the IVRS/IWRS specifications document and will be documented in the clinical study report).

5.5.1. Blinding

With the exception of the statistician who provides the randomization sequence, the IDMC statistician, the IDMC members, and the provisions in section 5.5.2, this study will remain blinded to all individuals until the pre-specified 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 weekly

injections of dupilumab or placebo starting at day 1. During weeks in which dupilumab is not administered in the q2w dosing regimen, patients will receive placebo.

Anti-drug antibody and drug concentration results will not be communicated to the sites, and the sponsor 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 the treatment assignment for a patient may be necessary due to a medical emergency, a serious adverse event (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). Details for emergency unblinding will be provided in the study manual.

- 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 at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2°C to 8°C 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

Any treatment administered from the time of informed consent 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:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

NOTE: If a patient receives treatment with systemic corticosteroids or other systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures

- Phototherapy
- Tanning in a bed/booth

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.

5.7.2.1. Cytochrome P450

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized.

However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (Abdel-Razzak 1993, Christensen 2012). Human peripheral blood mononuclear cells incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (Liptrott 2009).

Limited in vitro findings suggest that IL-4 and IL-13 may affect CYP levels and potentially activities. However, the clinical significance of these data is not fully understood. During the study treatment and at least up to the end of follow-up, investigators are cautioned to monitor clinical and laboratory signs that might indicate a potential drug-drug interaction in all patients receiving dupilumab concomitantly with narrow therapeutic index medications that are metabolized by CYP (see Investigator's Brochure for more details of such drugs). This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal, if needed.

For more details, refer to the study manual.

5.7.2.2. Prohibited Concomitant Medications or Procedures as Rescue

If medically necessary (eg, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator (see section 5.3 for details).

Blinded adjudication of concomitant medications may be performed to identify concomitant medications that confound study endpoints.

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 and Table 2.

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

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												
Safety:[7]														
Weight	X	X												
Height	X													
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Chest X-ray for TB[11]	X													
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV Ab, HBsAg, HBcAb, HBsAb, Hep C Ab	X													
Hepatitis B viral load[12]	X									X				
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[13]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[14]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

[1] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

[2] For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

[3] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[4] Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[5] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[6] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[7] To be collected before the injection of study drug.
[8] Assessments/procedures should be conducted in the following order: patient reported outcomes, investigator assessments, safety and laboratory assessments, administration of study drug.
[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).
[10] Select sites only - photograph AD area
[11] A chest x-ray will be performed to test for evidence of TB.
[12] Hepatitis B viral load will be measured only for patients who are HBsAg negative and HBsAb positive at the screening visit.
[13] Includes: antigen-specific IgE (region-specific allergen panels).
[14] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites.

Table 2: Schedule of Events – (Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination)

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6,7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hepatitis B viral load[11]				X					
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Total serum IgE				X	X	X	X	X	X
Antigen-specific IgE samples[12]				X			X	X	X
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[13]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[14]				X			X	X	X

[1] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

[2] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.

[3] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

[4] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[5] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[6] To be collected before the injection of study drug.

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

[8] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

[11] Hepatitis B viral load will be measured only for patients who are HBsAg negative and HBsAb positive at the screening visit

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites

[14] Patients with an ADA titer of ≥240 at the last study visit will be asked to return to the clinic to have additional samples collected for analysis (see section 6.3.4.2 for details and time points).

6.2. Study Visit Descriptions

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

1. Patient Reported Outcomes.
2. Investigator assessments (performed only by adequately trained investigators or sub-investigators; the same investigator or sub-investigator should perform all the evaluations for a given patient throughout the entire study period).
3. Safety and laboratory assessments.
4. Administration of study drug.

6.2.1. Visit 1/Screening/Day –35 to Day -1

After the patient has provided informed consent, the following information will be collected:

- Informed consent for optional assessments (for patients who consent to participate in the genomic sub-study)
- Inclusion/exclusion
- Medical history and concurrent illnesses
- Demographics
- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Training on IVRS
- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - Patient Oriented Eczema Measure (POEM)
  - Hospital Anxiety and Depression Scale (HADS)
  - Dermatology Life Quality Index (DLQI)
  - European Quality of Life-5 Dimensions (EQ-5D)
  - Asthma Control Questionnaire (ACQ-5)
  - Sinonasal Outcome Test (SNOT-22)
- Patient Global Assessment of Disease
- Vital signs
- Investigator's Global Assessment (IGA)

- Eczema Area and Severity Index (EASI)
- Global Individual Signs Score (GISS)
- SCORing Atopic Dermatitis (SCORAD)
- Body Surface Area of (BSA) involvement of atopic dermatitis
- Weight
- Height
- Physical examination
- Electrocardiogram (ECG)
- Chest X-ray for TB
- Laboratory testing:
  - HIV antibody
  - HBsAg
  - HBcAb
  - HBsAb
  - Hepatitis C antibody
  - Hepatitis B viral load (for patients who are HBsAg negative and HBsAb positive at the screening visit)
  - Hematology and Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - Thymus activation-regulated chemokine (TARC)
  - Total serum IgE
  - Antigen-specific IgE (region-specific allergen panels)
  - Highly sensitive C-reactive protein (hs-CRP)
  - Anti-nuclear antibody (ANA)
  - Anti-double-stranded DNA (anti-dsDNA)
  - Anti-thyroid peroxidase (anti-TPO)
  - Skin microbiome samples (select sites)
  - Research samples

6.2.2. Treatment Period

6.2.2.1. Visit 2/Baseline/Day 1

The following information will be collected:

- Inclusion/Exclusion
- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology and Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)

  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - DNA and RNA samples
  - Functional dupilumab pharmacokinetic (PK) sample
  - Anti-dupilumab antibody sample
- Randomization
- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.2. Visit 3/Week 1/Day 8 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Vital signs

- IGA
- EASI
- GISS
- SCORAD
- BSA
- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.3. Visit 4/Week2/Day 15 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA

- Laboratory testing:
  - TARC
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection
- Provide patient dosing diary
- Study drug dispensation

6.2.2.4. Visit 5/Week 3/Day 22 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.5. Visit 6/Week 4/Day 29 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM

  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.6. Visit 7/Week 5/Day 36 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.7. Visit 8/ Week 6/Day 43 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.8. Visit 9/Week 7/Day 50 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.9. Visit 10/ Week 8/Day 57 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD

- BSA
- Laboratory testing:
  - Hepatitis B viral load (for patients who are HBsAg negative and HBsAb positive at the screening visit)
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.10. Visit 11/Week 9/Day 64 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.11. Visit 12/Week 10/Day 71 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.12. Visit 13/Week 11/Day 78 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.13. Visit 14/Week 12/Day 85 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS

  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.14. Visit 15/Week 13/Day 92 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.15. Visit 16/Week 14/Day 99 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.16. Visit 17/Week 15/Day 106 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.17. Visit 18/End of Treatment/Week 16/Day 113 (±3 days)

The end of treatment at week 16 (visit 18) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hepatitis B viral load (for patients who are HBsAg negative and HBsAb positive at the screening visit)
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP

  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.3. Follow-up Period

6.2.3.1. Visit 19/Week 20/Day 141 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD

- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.3.2. Visit 20/Week 24/Day 169 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.4. Visit 21/End of Study Visit/Week 28/Day 197 (±3 days)

The end of study at week 28 (visit 21) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient global assessment of disease
- Patient global assessment of treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry

- Urinalysis
- Serum pregnancy test (WOCBP only)
- TARC
- Total serum IgE
- Antigen-specific IgE
- hs-CRP
- ANA
- Anti-dsDNA
- Anti-TPO
- Skin microbiome samples (select sites)
- Research samples
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

6.2.5. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 16) will be asked to return to the clinic for 2 visits: once for early termination assessments, and again at week 16 (primary endpoint visit), as described in section 6.2.2.17. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5

  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.6. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. During an unscheduled visit, any of the procedures noted may be performed, but not all are required.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight

- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

Assessments performed only at the screening and/or baseline visit include: medical history, medication history, demographics, diagnosis of chronic AD, chest X-ray to test for evidence of TB, HBsAg, HBcAb, HBsAb, anti-HIV antibody, and hepatitis C antibody.

6.3.2. 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 will be administered only to the subset of patients who fluently speak a language in which the assessment tool has been translated. These 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 POEM, HADS, DLQI, and EQ-5D).

6.3.2.1. Patient Assessment of Pruritus

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average 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 overall (on average) during the previous 24 hours?"
- 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.2. Patient-Assessed Pruritus Categorical Scale

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in 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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.3. 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 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 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 6.2.

The POEM is provided in the study reference manual.

6.3.2.4. 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 6.2.

The HADS is provided in the study reference manual.

6.3.2.5. Patient-Reported Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL (Badia 1999). The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. 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 6.2.

The DLQI is provided in the study reference manual.

6.3.2.6. Patient-Assessed EQ-5D

The EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement (ie, no problems, some problems, or severe problems) in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

The EQVAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)". This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

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 6.2.

The EQ-5D is provided in the study reference manual.

6.3.2.7. Patient Global Assessment of Disease

Patients will rate their overall wellbeing based on a 5-point Likert scale from poor to excellent. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent." Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.8. Patient Global Assessment of Treatment

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent". Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.9. Juniper Asthma Control Questionnaire

The 5-question version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.10. Sinonasal Outcome Test

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.11. Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.12. 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 6.2.

The IGA is provided in the study reference manual.

6.3.2.13. 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 6.2.

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

6.3.2.14. Body Surface Area Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 6.2.

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

6.3.2.15. 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. The GISS will be assessed at time points according to section 6.2.

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

6.3.2.16. SCORing Atopic Dermatitis

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). There are 3 components to the assessment: A = extent or affected body surface area, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see section 6.3.2.14) 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, 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 VAS, 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 6.2.

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

6.3.2.17. 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 (pre-dose). Subsequent photographs of the same area will be taken at week 16 (end of treatment) and week 28 (end of study).

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

6.3.3. Safety Procedures

6.3.3.1. Physical Examination

A thorough and complete physical examination will be performed at time points according to section 6.2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

6.3.3.2. Chest X-Ray

A chest x-ray will be obtained at the screening visit.

NOTE: A radiologist's (or qualified reader) interpretation (signed and dated) of the standard posterior-anterior and lateral chest x-ray must note the presence or absence of findings consistent with TB. A report indicating "normal chest x-ray" will be acceptable if the x-ray has been obtained within 3 months of the screening visit.

6.3.3.3. Weight and Height

Weight and height will be determined at time points according to section 6.2.

6.3.3.4. Vital Signs

Vital signs, including heart rate, blood pressure, body temperature, and respiration rate, will be collected pre-dose at time points according to section 6.2. Vital signs (blood pressure and heart rate) will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation.

6.3.3.5. Electrocardiogram

Electrocardiograms will be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to section 6.2. The ECG strips or reports will be retained with the source documentation, and the results will be documented in the electronic case report form.

Electrocardiogram results will be interpreted by a central reading center. Instructions for performing the assessment and transmitting ECG data are provided in the central ECG reference manual.

6.3.3.6. Laboratory Testing

Hematology, chemistry, urinalysis, and serum pregnancy testing samples will be analyzed by a central laboratory. The urine pregnancy test kit will be provided to the site by the laboratory.

Blood samples for serum chemistry and hematology testing will be collected to measure overall patient health at screening. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory. 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 6.2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[1]

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be reflexly measured when CPK >5X 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

Microscopic analysis will only be done in the event of abnormal dipstick results.

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

Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at time points according to section 6.2.

Testing for HIV antibody, HBsAg, HBcAb, HBsAb, and hepatitis C antibody will be performed at screening. Hepatitis B viral load will be measured at time points according section 6.2 (only for patients who are HBsAg negative and HBsAb positive at the screening visit).

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.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Samples for dupilumab concentration will be collected at time points listed in section 6.2.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in section 6.2.

Patients with an ADA titer of ≥240 at their last study visit (early termination or end of study) will be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months, until their titers fall below 240. Some patients who are negative for ADA at their last study visit will also be asked to return to the clinic within 6 to 12 months from their last dose of study drug to have additional ADA samples collected to maintain the blind.

6.3.5. Research Testing

Research assessments are performed for exploratory purposes only; results for assessments in the sub-sections below will not be reported in the clinical study report. Results will be reported separately from the clinical study report.

6.3.5.1. Research Samples

Research samples (serum/plasma) will be collected at time points according to section 6.2.

Use and Storage of Research Samples (Serum/Plasma)

Research serum and plasma samples will be collected to study the effects of the study drug on modulation of the IL-4 receptor and on atopic disease processes, as well as to study biomarkers that may have predictive utility for response to dupilumab treatment. Unused samples collected for drug concentration or ADA analyses may also be used for other research purposes. Remaining samples may be stored (up to 10 years) for future use in experiments related to AD or related diseases. If necessary, the samples may also be used to identify markers associated with toxicity.

6.3.5.2. Genomics Sub-Study - Optional

Patients will be asked to participate in an optional genomics sub-study. Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study informed consent form (ICF) before collection of the samples. Blood for DNA extraction should be collected on day 1/baseline (pre-dose), but may be collected at any study visit. RNA samples will be collected at time points according to section 6.2. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA and RNA samples for the genomics sub-study will be double-coded as defined by the ICH guideline E15. Sub-study samples may be stored for up to 10 years after the final date of the clinical study report and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to IL-4/13 pathway inhibition (via IL-4Rα blockade), atopic disease risk, prognosis and progression, or other clinical outcome measures. These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Genome-wide studies, including (but not limited to) single nucleotide polymorphism analyses and genomic sequencing may also be performed. If indicated, genomic analyses may also be performed to identify markers associated with toxicity.

6.3.5.3. Exploratory Biomarker Testing

Biomarkers to be analyzed in this study are: TARC, total serum IgE, antigen-specific IgE (region-specific, allergen-specific panels), *S. aureus* enterotoxin A-specific IgE, *S. aureus* enterotoxin B-specific IgE, hs-CRP, ANA, anti dsDNA, anti-TPO. Skin swab samples for skin microbiome testing may be banked. Samples will be collected at time points according to section 6.2. These are exploratory assessments to further the understanding of AD-associated biomarkers and the response to dupilumab treatment. The results of these tests will not be used to evaluate patient eligibility for study participation.

Thymus and activation regulated chemokine and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug. These results may also 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, and will be evaluated as an exploratory marker of efficacy. These markers may also be assessed for their potential value in predicting treatment response.

Staphylococcus aureus colonization and infection on the skin is a significant complication for many AD patients. To determine whether or not dupilumab treatment can reduce colonization and/or infection, exploratory samples for skin microbiome analyses may be banked. Non-invasive skin swab samples from lesional and non-lesional skin may be collected to characterize the skin microbiome diversity and *S. aureus* abundance. Skin swab samples for culturing (eg, semi-quantitative analysis of methicillin-sensitive and methicillin-resistant *S. aureus* colonization) may also be collected.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs 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 also be tested for predictive utility.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti-dsDNA, anti-TPO, and ANA) will be measured.

Detailed instructions for sample collection are provided in the laboratory manual.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

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

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

7.1.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.

- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as 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).

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 16 weeks 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 in this study include:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Severe ISRs that last longer than 24 hours
- Mycosis fungoides or other forms of cutaneous T cell lymphoma
- Any severe infection; any infection requiring treatment with parenteral antibiotics/anti-viral/anti-fungal agent; any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks; any clinical endoparasitosis; any opportunistic infection

Note: Generally, all uncommon, atypical, peculiar, or unusually persistent infections, especially viral infections, should be reported as AESIs.

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.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

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

Is there a reasonable possibility that the adverse event was 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

A list of factors to consider in assessing the relationship of AES to study, see Appendix 1.

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, AD history and characteristics, and medication history.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoint

During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries. As a result:

The primary endpoint is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Union (EU) and EU reference market countries, and Japan only, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

8.2.2. Secondary Endpoints

The key secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EU and EU reference market countries, and Japan, as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16

Other secondary endpoints are:

- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16

- Incidence of treatment-emergent adverse events (TEAEs) leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16

8.2.3. Other Endpoints and Assessments

- Absolute and percent change from baseline to week 16 in: EQ-5D, Patient Global Assessment of Disease and Patient Global Assessment of Treatment
- Distribution of disease severity scores (eg, IGA, EASI, SCORAD) and their change from baseline
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Absolute and percent changes in efficacy parameters through week 16
- Characterization of dupilumab serum concentrations through week 16
- Correlation analyses:
  - Body weight vs serum concentrations
  - Serum concentrations vs clinical outcomes
  - Body weight vs clinical outcomes
  - Association between baseline biomarkers (eg, TARC, total IgE) and clinical response
- Incidence of dupilumab ADA

8.3. Pharmacokinetic Variables

The PK variables may include, but are not limited to, the following:

- C_{trough} over time
- C_{last}
- T_{last}
- Time to steady state
- $C_{troughSS}$ - steady state trough concentration

8.4. Anti-drug Antibody Variables

ADA variables include status (positive or negative) and titer as follows:

- Total positive at any time
- Pre-existing immunoreactivity - a positive ADA response at baseline
- Treatment emergent - defined as either any positive response when baseline results are negative, or if any post treatment ADA response is ≥4-fold over baseline titer levels
- Persistently positive
- Transiently positive
- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

If a sample tests positive for ADA, the neutralizing activity of the ADA will be assessed.

9. STATISTICAL PLAN

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

Analysis variables are listed in section 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

Disease severity and region 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

To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total

with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo.

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 by the IVRS/IWRS at randomization (as randomized).

The per protocol set (PPS) includes all patient 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. The criteria of major protocol deviations are defined as the following:

- A patient who does not receive treatment as randomized
- Any major violations of efficacy-related entry criteria
- The percentage of a patient's compliance with study drug injection is <80% or >120% of the scheduled doses during the study treatment period

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). If a patient receives a dose regimen different to that assigned during the study, this patient will be considered as treated by the lowest active dose regimen. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

9.3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all randomized patients with at least 1 post-baseline drug concentration result.

9.3.4. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all randomized patients with at least 1 post-baseline ADA result.

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, median, standard deviation, 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. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

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 (region, disease severity) will be used for the percentage of patients with IGA 0 or 1 at week 16 or percentage of patients with EASI-75 at week 16.

To account for the impact of rescue medication on the efficacy effect:

For the binary efficacy endpoints, if rescue medication is used (see section 5.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.

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

Sensitivity analysis using 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.

In addition, the Cochran-Mantel-Haenszel method adjusted by randomization strata will also be performed on the observed variable regardless of rescue medication use and missing values.

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, different analysis methods will be used:

- For US and US reference market countries: Missing data from the randomized population will be imputed multiple times to generate a complete dataset at each imputation by using the multiple imputation (MI) Statistical Analysis Software (SAS) procedure with Markov Monte Carlo algorithm. These complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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.
- For EU and EU reference market countries, and Japan: A mixed-effect model with repeated measures (MMRM) will be used, which will account for the missing data. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. The MMRM model will provide baseline adjusted least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p-values for treatment comparisons by the appropriate time point-specific contrasts from the model. Additional details on the MMRM model will be provided in the SAP.

To account for the impact of rescue medication on the efficacy effect:

- Continuous efficacy endpoints: if a patient receives rescue medication that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue medication is initiated will be treated as missing.
- If a patient withdraws from the study, this patient will be counted as a non-responder for binary endpoints after withdrawal.

In addition to the MMRM model or the MI method described previously, sensitivity analysis using LOCF and MMRM/MI methods (if one of them is not described as the main analysis) will be conducted. Robustness of the MMRM model to departure from the missing-at-random assumption will be explored using sensitivity analysis based on the pattern mixture model. Additional details on these sensitivity analyses will be provided in the SAP.

9.5.2.3. Multiplicity Considerations

For US and US reference market countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

For EU and EU reference market countries, and Japan:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients achieving EASI-75 (≥75% reduction from baseline in EASI score at week 16 (this is not a secondary endpoint for the EU and EU reference market countries, and Japan as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of TESAEs from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

9.5.3. Safety Analysis

Safety analysis will be based on the SAF. This includes reported TEAEs and other safety information (ie, 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 pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug (day 1) to the end of the study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing 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 patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

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

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

9.5.3.2. Other Safety

Vital Signs

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

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.

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

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for 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 and calculated as:

(Date of last study drug injection – date of first study drug injection) + 7 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:

Treatment Compliance =

(Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) x 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

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

9.5.5. Analysis of Anti-Drug Antibody Data

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

9.5.6. Analysis of Quality of Life Data

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

9.5.7. 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-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 non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

The CRF data for this study will be collected with an electronic data capture 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, study drug supply
- EDC system – data capture/uploading and storing photographs
- Statistical Analysis Software (SAS) – statistical review and analysis
- ARGUS – a PVRM Safety System
- nQuery Advisor – sample size calculations

11. STUDY MONITORING

11.1. Monitoring of Study Sites

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

11.2. Source Document Requirements

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

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

11.3. Case Report Form Requirements

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

study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

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

12. AUDITS AND INSPECTIONS

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

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

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

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

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) must be kept in strict confidence.

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

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

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS dated 05 Feb 2015, and agree to abide by all provisions set forth therein.

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

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

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

(Signature of Investigator)	(Date)

(Printed Name)

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

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

No:

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

Yes:

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

NOTE: This list is not exhaustive.

STATISTICAL ANALYSIS PLAN

Title: A phase 3 confirmatory study investigating the efficacy and safety of dupilumab Monotherapy administered to adult patients with moderate-to-severe atopic dermatitis

Protocol: R668-AD-1334

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

Statistician: Haobo Ren, Ph.D.

Clinical Trial Manager: Jeannie Yo

Clinical Study Director: Marius Ardeleanu, MD

Author:

I Approve this Document
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List of abbreviations and definition of terms

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BAS	Biomarker analysis set
BSA	Body surface area
BUN	Blood urea nitrogen
CRF	Case report form
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonisation
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed effect model with repeated measures
NRS	Numerical rating scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term

qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

1 OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of this study. The SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for R668-AD-1334 study.

This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. These revisions will be based on blinded review of the study and data.

1.1 Background and Rationale

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus, xerosis, and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD.

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction. Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption. Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term

safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation. Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids. Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

IL-4 and IL-13 have been implicated as an important inflammatory component. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents.

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. There has been no evidence in the phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab.

This is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable. This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021).

1.2 Study Objectives

1.2.1 Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

1.2.2 Secondary Objectives

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD.

1.2.3 Modifications from the Statistical Section in the Final Protocol

Modifications from the Amended protocol 2 on Analyses of Secondary Efficacy Variables

- Multiple Imputation (MI) is used as the primary analysis method for continuous variables. MMRM will be used as a sensitivity analysis method for continuous variables. Sensitivity analysis by pattern mixture model will not be performed.
- Add the endpoint "Proportion of patients with improvement (reduction) of pruritus NRS ≥4 from baseline to week 16" as a key secondary endpoint
- Change the order of the hierarchy for the secondary endpoints, i.e. move the endpoint "Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16" prior to the endpoint of "Incidence of TESAEs from baseline through week 16".

2 INVESTIGATIONAL PLAN

2.1 Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study. Eligible patients will be randomized in a 1:1:1 ratio to qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by country.

2.2 Sample Size and Power Considerations

To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size was increased to 600 in total with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between

dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. Power calculation was implemented by nQuery Advisor 7.0.

2.3 Study Plan

The study consists of a screening period, a treatment period and a follow-up period as presented below:

Screening	**Treatment Period**[1,2]			**Follow-Up**[3]
V1	V2	V3 to V17 (qw)	V18	V19 to V21 (q4w)
	Baseline	W1 to W15	End of Treatment[3]	End of Study
(Day –35 to Day -1)	(Day 1)	(Day 8 to Day 106)	(Day 113)	(Day 141 to Day 197)

[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out. Patients may be re-screened 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 at least twice daily for at least the 7 consecutive days immediately before randomization and continue throughout the study. To allow adequate assessment of skin dryness, moisturizers should not be applied on the areas of non-lesional skin used for such assessments for at least 8 hours before the clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study

site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Appendix 10.2).

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in the maintenance study, R668-AD-1415. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study (R668-AD-1225), but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Patients with an ADA titer of ≥240 at their last study visit and some patients who are negative for ADA at their last study visit may be asked to return to the clinic to have additional ADA samples collected for analysis. See Section 4.7 for details.

3 ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following population of analysis will be used for all statistical analysis.

3.1 Efficacy Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). This is the primary analysis population for efficacy analysis.

Patient who was randomized more than once will be analyzed as distinct patients based on the treatment allocated at randomization.

Patients who temporarily or 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 and complete all study assessments per the study schedule.

3.2 Per Protocol Analysis Set

The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations.

A major efficacy-related protocol violation is one that may affect the interpretation of study results. The criteria of major efficacy-related protocol deviation are defined as following:

- Patients who did not receive treatment as randomized, which are defined as
  - patients on placebo but accidentally exposed to dupilumab,
  - patients on dupilumab receiving > 2 injections different from planned treatment
- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
  - Inclusion criteria 3, 4, 5 and 6
  - Exclusion criteria 3, 4, 5, 6, 7 and 8
- Patients who received <80% or >120% of the scheduled doses during the study treatment period

The PPS will be finalized before the database lock.

3.3 The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive any study drug, and will be analyzed as treated.

The actual treatment group is defined following rules below:

- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen group
- For patients on dupilumab accidentally receiving ≤ 2 vials different from the planned treatment, the actual treatment group allocation for as-treated analysis will be the planned dupilumab dose / regimen
- For patients on dupilumab receiving > 2 vials different from planned treatment, the actual treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen group

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized

The safety analysis will be based on the SAF.

3.4 The Pharmacokinetic Analysis Set (PKAS)

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.

3.5 The ADA Analysis Set (AAS)

The ADA population will consist of all treated patients who received any study drug and who had at least one qualified ADA result after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

4 ANALYSIS VARIABLES

4.1 Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age at screening (year), age group (<65, >=65), Sex, Ethnicity, Race, Region (Americas, Asia Pacific, East Europe, West Europe), Country, Baseline Weight (kg), Height (m), and BMI (kg/m^2)
- Baseline characteristics: Duration of AD disease, Pruritus numerical rating scale (NRS) for maximum or average itch intensity, Pruritus categorical scale, Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, Global Individual Signs Score (GISS), SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) Involvement of Atopic Dermatitis, Patient global assessment of disease status, Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Itchy Quality of Life (QoL), EQ-5D and Hospital Anxiety and Depression Scale (HADS), Asthma Control Questionnaire (ACQ-5), and Sinonasal Outcomes Test (SNOT-22)

4.2 Medical History and Atopic Disease Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO. Information on conditions related to AD includes diagnosis of AD and AD treatment history, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy hives and other allergies due to medications, animals, plants, mold, dust mites, etc. Recent AD history within 1 year before the screening visit is also collected with information of number of AD flares and episodes of skin infections requiring pharmacological treatment.

4.3 Pre-treatment / Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the EOS visit.

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

Prohibited concomitant medications/procedures: Treatment with the following concomitant medications is prohibited during the study:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

Rescue treatments (medications/procedures): 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.

Patients who receive rescue treatment during the study treatment period will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment.

If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) study treatment will be immediately discontinued.

After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure.

4.4 Efficacy Variables

4.4.1 Primary Efficacy Variable

During discussions with health authorities, different health authorities requested different primary endpoints, although the conduct of the study will be the same for all countries. As a result, the primary endpoint for US and US reference market countries is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Union (EU) and EU reference market countries, as well as Japan, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
-

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument to rate AD disease severity globally in clinical studies. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration. IGA score will be assessed at every scheduled and unscheduled clinic visit.

Eczema Area and Severity Index (EASI)

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 score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 =

1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section.

The EASI will be collected at every scheduled and unscheduled clinic visit.

4.4.2 Secondary Efficacy Variables

The key secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA EU and EU reference market countries, as well as Japan as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16

Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average 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 overall (on average) during the previous 24 hours?"
- 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

For each day, if there are multiple NRS of the same question (average or worst) scores collected on a same day, take average of all the scores collected.

The baseline NRS is defined as the prorated average of the NRSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline NRS, The mean weekly NRS is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 +

score3)/3. The baseline NRS and mean weekly NRS will be calculated for average itch intensity and peak itch intensity separately.

Other secondary efficacy endpoints are:

- Percent change in EASI score from baseline to week 16
- Proportion of patients with EASI-90 at week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Percent change from baseline to week 16 in GISS
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in weekly average of peak daily pruritus NRS
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 every scheduled and unscheduled clinic visit.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). The extent of AD is assessed by the Investigator as a percentage of each defined body area 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 (erythema, oedema / papulation, excoriations, lichenification, oozing / crusts and dryness) of AD is assessed by the Investigator 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 (VAS), 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. The maximum SCORAD score is 103.

Patients will undergo this assessment at every scheduled and unscheduled clinic visit.

Global Individual Signs Score (GISS)

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally by the Investigator (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe) using the EASI severity grading criteria. The cumulative score is the sum of the four components, which will be ranged from 0 to 12. The GISS will be assessed at every scheduled and unscheduled clinic visit.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire (Badia 1999) used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on Quality of Life (QoL). The format is a simple response to 10 items, which assess QoL over the past week. For each item, the scale is rated as follows: 0='not at all'='not relevant'; 1='a little'; 2='a lot'; 3='very much'='yes' in question 7, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. The DLQI will be assessed at every scheduled and unscheduled clinic visit.

- Handling missing items from DLQI

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
ii. If two or more questions are left unanswered the questionnaire is not scored.
iii. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
iv. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
v. If two or more response options are ticked for one question, the response option with the highest score should be recorded.
vi. The DLQI can be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

Hospital Anxiety and Depression Scale (HADS)

The HADS is a general Likert scale used to detect states of anxiety and depression (Bjelland 2002). The 14 items on the questionnaire include 7 that are related to anxiety (odd number questions) and 7 that are related to depression (even number questions). Each item on the questionnaire is scored from 0 (the best) to 3 (the worst) according to the content of the item; a person can score between 0 and 21 for either anxiety or depression. A high score is indicative of a poor state. For each sub-scale: if one question is missing, 7 times the prorated mean of the remaining six questions is imputed. If more than one question is missing, then the subscale is missing. The total score is the sum of two sub-scores. HADS will be assessed at every scheduled and unscheduled clinic visit.

Patient Oriented Eczema Measure (POEM)

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 patient response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping). Each item is a 5-point scale (from 0='no days' to 4='every day'). The total score is the sum of the 7 items which is ranged from 0 to 28 and reflects disease-related morbidity; a high score is indicative of a poor QOL. The POEM will be assessed at every scheduled and unscheduled clinic visit.

DLQI, HADS and POEM will be administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

4.4.3 Other Efficacy Variables

Other efficacy variables include:

- Change and percent change from baseline to week 16 in: EQ-5D, Patient Global Assessment of Disease and Patient Global Assessment of Treatment
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Change and percent changes in efficacy parameters through week 16

Pruritus Categorical Scale (PCS)

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in clinical studies of AD and has less of a "middling" effect (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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not

complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

For each day, if there are multiple PCS scores collected on the same day, the maximum (worst) of all the scores collected will be chosen. For each week, calculate round prorated average of collected scores for Category Score. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3 round to 1.0.

The baseline PCS is defined as the round prorated average of the PCSs reported continuously for 7 days right before the baseline visit.

Patient Global Assessment of Disease Status

Patients will rate their overall wellbeing based on a 5-point Likert scale. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing". Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5). Patients will undergo this assessment at the following visits: screening, day 1/baseline (pre-dose), and days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

Patient Global Assessment of Treatment Effect

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5). Patients will undergo this assessment at the following visits: days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

EQ-5D

The EQ-5D is a standardized measure of health status developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economic appraisal (Greiner 2005). The EQ-5D as a measure of health related QOL, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health."

The 5 dimensional 3-level systems are converted into a single index utility score. Values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model and weighted according to the social preferences of the UK population. The minimum value for the single index utility score is –0.594, The EuroQol Visual Analogue Scale (EQVAS) records the respondent's self-rated health on a vertical visual analogue scale. The VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcomes as judged by the individual respondents. EQ-5D self-reported VAS data

generates information on the self-perceived overall health-related quality of life. Appendix 10.4 provides the SAS code to derive the index utility score using UK based population. EQ-5D will be assessed at every scheduled and unscheduled clinic visit.

EQ-5D will be administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

4.5 Safety Variables

4.5.1 Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, latest version).

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal (investigational) product.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

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

The pre-treatment period is defined as the period from the subject providing informed consent up to the first dose of study drug. The treatment and follow-up period is defined as the period from the administration of first study dose to the EOS visit.

The pre-treatment AE and treatment emergent AE (TEAE) are defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during pre-treatment period.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered as TEAEs.

4.5.2 Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Blood samples for serum chemistry and hematology testing will be collected at screening (day -35 to day -1), baseline (day 1), on days 29, 57, 85, 113, 197 (EOS) or ET, and at unscheduled visits. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory.

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[1]

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be reflexly measured when CPK >5X the ULN

Hematology with Differential

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

Urinalysis

Urine samples for urinalysis will be collected to measure overall patient health at screening, and will also be collected at (day -28 to day -1), baseline (day 1), on days 113, 197 (EOS) or ET, and at unscheduled visits.

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

Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Evidence of pregnancy
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5 \times 10^3$ μL
  - Platelet count $\leq 50 \times 10^3$ μL
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3x upper limit of normal (ULN) with total bilirubin >2x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5x ULN (for more than 2 weeks)
- Other reasons that may lead to the permanent discontinuation of study treatment include: treatment with any prohibited concomitant medication or procedure

Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.0 \times 10^3/\mu L$ but $>0.5 \times 10^3/\mu L$
  - Platelet count $\leq 100 \times 10^3/\mu L$ but $>50 \times 10^3/\mu L$
  - Creatine phosphokinase (CPK) >10x ULN
- Other intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (eg, cyclosporine, methotrexate, azathioprine, mycophenalate-mofetil, Janus kinase inhibitors, biologic agents, etc)

4.5.3 Vital Sign Variables

The following vital signs parameters will be collected:

- Weight (kg) and height (cm)
- Respiratory rate (bpm)
- Heart rate (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (^{o}C)

Weight is determined at screening and day 1/baseline, and days 113, 197 (EOS), any unscheduled visit, or ET. Height is only measure at screening. Other vital signs are collected pre-dose at every scheduled and unscheduled clinic visit. Blood pressure and heart rate will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation.

4.5.4 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] =QT/[$RR^{0.33}$] and QTc Bazett [QTcB]=QT/[$RR^{0.5}$]) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at screening, days 113 and 197 (EOS) or ET.

4.5.5 Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.
A thorough and complete physical examination will be performed at screening, day 113, and day 197 (EOS) or ET.

4.6 Pharmacokinetic (PK) Variables

- Characterization of functional dupilumab concentrations in through week 16
- Correlation analyses:
    - Body weight vs functional dupilumab concentrations
    - Functional dupilumab concentrations vs clinical outcomes

Samples for drug concentration will be collected at day 1/baseline (pre-dose), days 15, 29, 57, 85, 113, 197 (EOS), unscheduled visits and ET. Pharmacokinetic variables may include but not limited to C_{trough} over time, $C_{last,}$ $T_{last,}$ time to steady state and $C_{troughSS}$ (steady state trough concentration).

4.7 Antibody (ADA) Variable

Serum samples for anti-dupilumab antibody assessment will be collected at day 1/baseline and at days 15, 29, 57, 113, and 197 (EOS), unscheduled visits and ET.

Incidence of positivity in the ADA assay will be assessed as absolute occurance (n) and percent of patients (%), presented by active treatment groups. Listing of all ADA titer levels will be provided for patients positive in the ADA assay.

ADA variables include ADA status (positive or negative) and titer as follows:

- Total subjects negative in the ADA assay at all times
- Total subjects positive in the ADA assay at any time.
- Total subjects with preexisting immunoreactivity
    - Pre-existing immunoreactivity- defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.
- Subjects with treatment emergent response in the ADA assay (ADA Incidence)
    - Treatment emergent - defined as either a positive response in the ADA assay post first dose when baseline results are negative, OR if any post first dose positive response in the ADA assay is greater than or equal to 4-fold over baseline titer levels. The treatment emergent responses will be further characterized into Persistent and Transient
    - Persistent Response- Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by at least a 12- week period OR the last collected samples is positive in the ADA assay
    - Transient Response- Any treatment emergent ADA positive response that is not considered persistent.
- Titer Values (Titer value category)
    - Low (titer <1,000)
    - Moderate (1,000 ≤ titer ≤ 10,000)
    - High (titer >10,000)

ADA positive samples will be further characterized for the presence of neutralizing antibody responses.

Patients with an ADA titer of ≥240 at their last study visit (early termination or end of study) may be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months, until their titers fall below 240. Some patients who are negative for ADA at their last study visit may also be asked to return to the clinic within 6 to 12 months from their last dose of study drug to have additional ADA samples collected to maintain the blind.

4.8 Other Variables (QoLs and Biomarkers)

Juniper Asthma Control Questionnaire (ACQ-5)

The 5-question version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of asthma and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment,

6= maximum impairment). A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ, any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing value, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

Sinonasal Outcome Test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

It contains 22 items. The total score of the SNOT-22 is calculated by summation of all the item scores. The total score ranges from 0 to 110. The MCID is equal to 8.9. For patients where some SNOT-22 items were incomplete, a total score for the SNOT-22 will be imputed as mean of the completed items, providing at least 50% of items have been completed. If more than 50% of items are missing, the total score will be considered as missing.

Twenty two items are classified into five domains as in following table. The score for each domain is the sum of response to each question in that domain. Domain score will be imputed as mean of the completed items in that domain, providing at least 50% of items in that domain have been completed.

Domain	Items
Nasal	2, 3, 4, 6, 7, 12
Ear	8, 9, 10
Sleep	13, 14, 15, 16
General and practical	1, 5, 11, 17, 18, 19
Emotional	20, 21, 22

Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at day 1/baseline, days 29, 57, 85, 113, 141, 169, 197 (EOS), unscheduled visits and ET.

Biomarker: Association between baseline biomarkers (eg, TARC, total IgE) and clinical response

Biomarkers to be analyzed in this study are:

- TARC and total serum IgE
- antigen-specific IgE
- hs-CRP, ANA, anti dsDNA, anti-TPO

TARC and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs in circulation, indicating they are atopic. To further understand atopy in this patient population, region-specific, allergen-specific IgE panels will be performed.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti-dsDNA, anti-TPO, and ANA) will be measured.

Samples will be collected at time points according to the schedule in 10.2.

5 STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

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

5.1 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups based on FAS. Listing of demographics and baseline characteristics will be presented.

5.2 Medical and AD History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

Medical history will be listed, sorted by treatment groups based on the SAF.

5.3 Pre-treatment/Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications/procedures, prohibited medications/procedures and rescue medications/procedures will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined dupilumab treatment groups.

Listing of pre-treatment medication and concomitant medications will include generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications

started on or after treatment, the study day onset = date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, route.

The detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized by topical and systemic groups. Kaplan Meier curves for time to first rescue use will be generated.

The compliance of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group.

5.4 Subject Disposition

The following summaries by table will be provided:

- The total number of screened patients
- 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 treatment and the reasons for the discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation

The following listings will be provided:

- Listing of subject disposition including: date of randomization, date of the last visit, received dose, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized, including the patients who missed active study drug doses to the point that their cumulative exposure ends up being closer to another study regimen that is different from the one to which they had been randomized (e.g., a patient randomized to 300 mg qw who missed 30-50% of doses will be closer to 300 mg q2w than to the originally assigned 300 mg qw)
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation, summary tables of reasons will be provided
- Summary table with listing of protocol deviations will be provided

5.5 Dose administration

The compliance with protocol-defined investigational product will be calculated as follows:

Treatment Compliance= (Number of injections during exposure period) / (Number of planned injections during exposure period) x 100%

Loading doses for the same patient will be counted as 1.

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information, and whether or not the total dose is administered for each dose will be presented.

If subjects received treatment different from the randomized treatment or stopped treatment due to an AE, or overdosed, the listings will be provided.

5.6 Treatment Exposure and Observation Period

The duration of treatment exposure period during the study is calculated as:

(Date of last study drug injection – date of first study drug injection) + 7

regardless of unplanned intermittent discontinuations. The duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums.

The duration of observation period during the study is calculated as:

(Date of the last visit – date of the first study medication dose) +1.

The number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest is specified as:

≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 43 days, ≥50 days, ≥ 57 days, ≥ 64days, ≥ 71 days, ≥ 78 days, ≥ 85 days, ≥99 days, ≥113 days, ≥127 days, ≥141 days, ≥155 days, ≥169 days, ≥183 days, ≥197 days.

5.7 Analyses of Efficacy Variables

For all efficacy variables, the analysis will be comparisons of each dupilumab regimen and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested for each dupilumab regimen group and the placebo group:

H0: $p_{dupilumab} = p_{placebo}$, where p stands for the percent of responders in a treatment group

H1: $p_{dupilumab} \neq p_{placebo}$.

The analyses of efficacy variables are summarized in Appendix 10.1.

5.7.1 Analysis of Primary Efficacy Variable

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

Handling of dropouts or adjudicated rescue treatment or missing value for the binary response variables

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

To account for the impact of rescue treatment on the efficacy effect:

For the binary efficacy endpoints, if rescue treatment is used (see Section 4.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.

If the patient has the missing value at week 16, then it will be counted as a non-responder at week 16.

Sensitivity analysis

1. Last observation carried forward (LOCF) approach after censoring for rescue treatment use or study withdrawal 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.
2. All observed data, no matter if rescue treatment is used or data is collected after withdrawal will be included for the primary endpoint. Patients with missing value will be counted as non-responder.
3. Same as the main statistical analysis but including only patients in PPS.

Subgroup analyses

Subgroup analyses will be performed for the primary efficacy variable by:

- Baseline disease severity [moderate (IGA=3) and severe (IGA=4)]
- region/country
- Baseline body weight (< overall median, >= overall median)
- Age (<65, 65-75 and >75)
- Gender,
- Ethnicity
- Race
- Baseline EASI (>30, <=30)
- Baseline peak NRS (<7, >=7)
- Duration of AD (<overall median, >=overall median)
- Previous usage of cyclosporine (Yes, No)
- History of asthma (Yes, No)
- History of nasal polys (Yes, No)

5.7.2 Analyses of Secondary Efficacy Variables

The binary secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoints.

The endpoint "Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16" will only be analyzed for patients with baseline peak pruritus NRS ≥4.

The continuous endpoints will be analyzed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model. Missing data from the FAS will be imputed 50 times to generate 50 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. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2. The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, randomization strata (region, disease severity), and relevant baseline.

The week 16 data of each of the 50 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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 50 analyses using Rubin's formula.

Patients' efficacy data through week 16 after the rescue treatment usage will be set to missing first, and then be imputed by the multiple imputation method.

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, the baseline value and the randomization strata
- Measured endpoint values from every clinic visit up to week 16

Categorical variables included in above model (i.e., treatment group and randomization strata) are not expected to be missing.

To account for the impact of rescue treatment on the efficacy effect:

- Continuous efficacy endpoints: if a patient receives rescue treatment that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue treatment is initiated will be treated as missing.

Sensitivity analysis

In addition to the MI method described previously, sensitivity analyses for the continuous endpoints for EASI and/or Pruritus NRS will be conducted as described below.

1. The sensitivity analysis based on all observed data no matter if rescue treatment is used or data is collected after withdrawal using MI method will be performed.
2. This sensitivity analysis will use a mixed-effect model repeated measures (MMRM). The model will include factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within-patient errors. Denominator degrees of freedom will be estimated using approximation of SATTERTH. The efficacy data will be set to missing after rescue treatment is used. Afterwards no imputation will be made.

   The MMRM model will provide least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error, confidence interval, and the p-value for treatment comparisons. The graph of LS-mean +/- se by visit will be provided.
3. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue treatment is used. The LOCF method will then be used to impute missing values.

Analysis of incidence of TEAE-related variables

- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

These endpoints will be analyzed for patient in SAF. The period from baseline through week 16 is defined as from study day 1 to study day 113. The Cochran-Mantel-Haenszel test adjusted for randomization strata (region, disease severity) will be used for the percentage of patients with events described above through week 16.

In addition, a negative binomial regression model will be used to assess treatment differences in number of events described above. The model will include the total number of events as response variable, and treatment group and randomization strata as covariates. Log-transformed observation duration will be the offset variable. Pairwise comparisons of the annualized event rates between each dose of dupilumab and placebo will be derived by testing each active dose group versus placebo separately. Two-sided 95% confidence intervals of the rate ratio will be provided. The estimated events rate and its 2-sided confidence intervals will be provided for each treatment group.

Multiplicity Considerations

For US and US reference market countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

For EU and EU reference market countries, as well as Japan:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients achieving EASI-75 (≥75% reduction from baseline in EASI score at week 16 (this is not a secondary endpoint for the EU and EU reference market countries, as well as Japan as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16
- Incidence of TESAEs from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

5.7.3 Analyses of Other Efficacy Variables

Analyses of categorical variables will be similar to the primary analysis; analyses of continuous variables similar to the secondary analyses.

In addition, the following endpoints will be analyzed:

- Number (%) of patients with HADS-A or HADS-D >=8 at week 16
- Number (%) of patients with HADS-A or HADS-D >=11, at week 16
- Number (%) of patients with HADS-A or HADS-D >=8 at week 16 for those patients with HADS-A or HADS-D >=8, or HADS-A or HADS-D >=11, at baseline
- Number (%) of patients with HADS-A or HADS-D >=11 at week 16 for those patients with HADS-A or HADS-D >=11, at baseline

5.8 Analysis of Safety Data

The summary of safety and tolerance will be performed based on SAF.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs, and 12-lead ECG.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables, vital signs and ECG are defined in appendix 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

5.8.1 Adverse Events

Listings of Pre-treatment AEs, TEAEs and serious TEAEs will be generated.

The following variables will be included in the listing:

- Patient id
- Treatment group
- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)
- Verbatim Term
- AE start date and end date/ongoing (using both calendar days and study days)
- AE Duration
- Relationship of AE to study drug: unrelated or related
- Action taken: Dose withdrawn temporarily, Dose reduced, Dose withdrawn permanently, Dose not changed, Not known or Not applicable
- Severity: using a 3–point scale (mild, moderate, or severe)
- Treatment: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with sequelae, recovering/ resolving, not recovered/not resolved, fatal or unknown

Listing of TEAEs resulting in death and study discontinuation will also be generated

Number and proportions of subjects reporting TEAEs will be summarized, sorted by decreasing frequency of SOC and PT for the highest dose level.

Summaries of TEAEs will include:

- Proportion of subjects with at least one TEAEs
- Proportions of subjects with at least one TEAEs by SOC/PT
- Proportions of subjects with at least one TEAEs by SOC/HLT/PT
- Proportions of subjects with at least one TEAEs by PT
- Proportion of subjects with at least one TEAEs by severity by SOC/PT
- Proportion of subjects with at least one TEAEs related to study medication by SOC/PT

- Proportion of subjects with at least one serious TEAEs by SOC/PT
- Proportion of subjects with TEAEs leading to discontinuation of study treatment by SOC/PT

Summary of the most frequent (>=5%) TEAEs by SOC, HLT, PT, respectively, in the aggregate dupilumab groups and in the overall study population will be provided.

SAEs/AESI during treatment and follow up period will be listed.

5.8.2 Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with abnormal lab value during study whose screening and baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs during study, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by subject and visit will be provided.

5.8.3 Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings will be provided with flags indicating the treatment-emergent PCSVs, depending on data.

5.8.4 Physical Exams

The number (n) and percentage (%) of subjects with abnormal physical exams will be summarized at baseline, end of treatment period and end of study by treatment group. A summary of treatment-emergent abnormal findings will be provided.

5.8.5 Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings will be provided with flags indicating PCSVs, depending on data.

5.9 Analysis of Pharmacokinetic Data

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

5.10 Analysis of ADA Data

The ADA variables will be analyzed using descriptive statistics. Drug concentration data will be examined and the potential influence of ADAs on concentration-time profiles will be evaluated. Assessment of impact of ADA on safety and efficacy will be provided.

5.11 Analysis of Other Variables (QoLs and Biomarkers)

Changes or percentage changes from baseline to each measurement visit in ACQ-5 and SNOT-22 will be summarized. Number of sick Leave/missed school days from each assessment will be summarized by treatment group.

Descriptive statistics for the observed values, change from baseline and percent change from baseline values by treatment and visit will be provided for the following biomarker variables:

- TARC (screening, days 1, 15, 29, 57, 85, 113, 197)
- total serum IgE (screening, days 1, 29, 57, 85, 113, 141, 169, 197)
- antigen-specific IgE (screening, days 1, 29, 57, 85, 113, 197)
- hs-CRP, ANA, anti dsDNA, anti-TPO (screening, days 1, 57, 85, 113, 197)

The Wilcoxon signed-rank test will be used to test if the change or percentage change from baseline value is significantly different from zero. P-value will be reported.

Exploratory analyses for the difference between dupilumab groups and placebo on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group as fixed effects, and the relevant baseline values as covariate. Missing value will be imputed by LOCF method for visits between post-baseline to visit 18 (week 16). After visit 18, no imputation will be made. P-value for difference from placebo will be provided.

Correlation of baseline TARC (measured value), IgE (measured value), and positivity to at least one antigen-specific IgE with the following clinical endpoints will be explored using the Spearman's rho tests. Both Spearman correlation coefficients and p-value will be reported from the model.

- IGA 0-1 at week 16
- EASI-75 at week 16
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS $\geq$3 from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD

Shift tables from baselines status to post-baseline status for hs-CRP, ANA, anti dsDNA and anti-TPO variables will be provided by treatment group.

All above analyses will be performed on the FAS for

- All observed data, no matter if rescue treatment is used or data is collected after withdrawal
- All observed data with censoring after rescue treatment use or study withdrawal

6 DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1 Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of NRS is defined in Section 4.2.

6.2 General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3 Data Handling Convention Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAE. For example, if the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is ‘D’.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to in line with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of follow up date. Imputation flag is 'Y'.

6.4 Analysis Visit Window

All available values obtained between 2 planned visits including unscheduled measurements will be pooled to the analysis visit window according to the following definition:

Visit	Target Day	Analysis Time Window
Screening (1)	<1	<1
Day 1 (Baseline, 2)	1	1
Right after Baseline (3)	d_3	[2, flooring((d_3 + d_4+1)/2)]
…	….	…
i (i>3)	d_i	…
i+1	d_{i+1}	(ceiling((d_i + d_{i+1})/2), flooring((d_{i+1} + d_{i+2}+1)/2)]
i+2	d_{i+2}	…
…	….	…
Last	D_{last}	(ceiling((d_{last-1} + d_{last})/2), flooring((3d_{last} - d_{last-1})/2)]

In the event of multiple measurements of the same test in the same window, if the measurements are from different categories, the priority order is ET, scheduled then unscheduled visit. For the measurements in the same category, the value measured nearest to the target day will be assigned to the window; if they are at the same distance to the target day, the latest one will be used. Laboratory, vital sign and ECG data collected from unscheduled visits will be used in PCSV analysis, and will be pooled into analysis window for the by visit analysis. The above analysis-window algorithm applies also to the efficacy endpoints.

For the ePRO data collected daily via IVRS, the analysis visit windows will be implemented following the procedures below:

Step 1: Derive the study day,

If diary date >= 1st injection date, diary study day=diary date – 1st injection date +1; Otherwise diary study day=diary date – 1st injection date

Step 2: Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc.

7 INTERIM ANALYSIS

No interim analysis is planned.

8 SOFTWARE

All analyses will be done using SAS Version 9.2 or above.

9 REFERENCES

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10 APPENDIX

10.1 Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16;	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Secondary continuous variables	FAS	MI	MMRM, ANCOVA with LOCF	Yes for EASI and NRS endpoints	Line plot
Categorical variables	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test / LOCF	Yes for EASI and NRS endpoints	Histogram

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2 Schedule of Events

Screening, Baseline, and Treatment Period

Study Procedure	Screening	Baseline	Treatment Period											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												
Safety:[7]														
Weight	X	X												
Height	X													

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)	**-35 to -1**	**D1**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)			**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV Ab, HBsAg, HBcAb, Hep C Ab, TB[11]	X													
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[12]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[13]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

[1] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

[2] For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

[3] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[4] Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[5] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[6] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[7] To be collected before the injection of study drug.

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

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

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

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites.

Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination

Study Procedure	Treatment Period[1]				Follow-up Period		EOS[1]	Unscheduled Visit[2] (if applicable)	Early Termination (if applicable)
Visit (V)	V15[3]	V16[3]	V17[3]	V18	V19	V20	V21		
Week (W)	W 13	W 14	W 15	W 16	W 20	W 24	W 28		
Day (D)	D92	D99	D106	D113	D141	D169	D197		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6, 7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X
Total serum IgE				X	X	X	X	X	X
Antigen-specific IgE samples[11]				X			X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[12]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[13]				X			X	X	X

[1] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

[2] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.

[3] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

[4] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[5] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[6] To be collected before the injection of study drug.

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

[8] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

[11] Includes: antigen-specific IgE (region-specific allergen panels).

[12] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites

[13] Patients with an ADA titer of ≥240 at the last study visit will be asked to return to the clinic to have additional samples collected for analysis

10.3 Criteria for Treatment-Emergent Potentially Clinical Significant Value

Parameter	PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(>35% Total Bilirubin **and** TBILI>1.5 ULN), and baseline (Total Bilirubin <=35% **or** TBILI <=1.5 ULN)	Conjugated bilirubin dosed on a case-by-case basis.

Parameter	PCSV	Comments
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L ≥30% to < 100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Creatinine Clearance (Cokcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 -<30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 - < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 - < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Use is optional. FDA draft guidance 2010 Four independent criteria, will provide additional shift table if needed
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hyponatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.

Parameter	PCSV	Comments
Lipasemia	≥3 ULN and < 3ULN at baseline	
Amylasemia	≥3 ULN and < 3ULN at baseline	
Glucose		
Hypoglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black);	Increase in WBC: not relevant.
	<2.0 Giga/L and >=2.0 Giga/L at baseline (Black)	
	≥16.0 Giga/L and < 16 Giga/L at baseline	To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black);	International Consensus meeting on drug-induced blood cytopenias, 1991.
	<1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female.	Three criteria are independent.
	≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
	Decrease from Baseline ≥20 g/L	
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male; ≤0.32 v/v and > 0.32 v/v at baseline forFemale	Two Criteria are independent
	≥0.55 v/v and < 0.55 v/v at baseline for Male; ≥0.5 v/v and < 0.5 v/v at baseline for Female	

Parameter	PCSV	Comments
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	

Parameter	PCSV	Comments
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSV to be identified in individual subjects/patients listings. 5 independent criteria

10.4 SAS code for EQ-5D index utility scoring

```
/*=================================================================*/;
/*  Aim                       : Derive the EQ5-D index (utility)
*/;
/*  Source for the algorithm : scoring EQ-5D health states (Rosalind Rabin
*/;
/*            (cf. G:\_HE\PRO questionnaire\EQ5D\scoring\YorkTariffx.doc)
*/;
/*  Note                      : UK based population (Dolan, 1997)
*/;
/*  Author                    : Elisheva Smadja
*/;
/*=================================================================*/;

data EUROQOL;   set temp;
   profil= (10000*eqq1cd)+(1000*eqq2cd)+(100*eqq3cd)+(10*eqq4cd)+eqq5cd;
   eq5d=1;
**********Mobility*********;
if eqq1cd=2     then eq5d=eq5d-0.069;
if eqq1cd=3     then eq5d=eq5d-0.314;
********Self-care**********;
if eqq2cd=2     then eq5d=eq5d-0.104;
if eqq2cd=3     then eq5d=eq5d-0.214;
******Usual activities*****;
if eqq3cd=2     then eq5d=eq5d-0.036;
if eqq3cd=3     then eq5d=eq5d-0.094;
*****Pain/discomfort******;
if eqq4cd=2     then eq5d=eq5d-0.123;
if eqq4cd=3     then eq5d=eq5d-0.386;
*****Anxiety/depression*****;
if eqq5cd=2     then eq5d=eq5d-0.071;
if eqq5cd=3     then eq5d=eq5d-0.236;

if (eqq1cd ne 1 or eqq2cd ne 1 or eqq3cd ne 1 or eqq4cd ne 1 or eqq5cd ne 1)
                then eq5d=eq5d-0.081;
if (eqq1cd=3 or eqq2cd=3 or eqq3cd=3 or eqq4cd=3 or eqq5cd=3)
                then eq5d=eq5d-0.269;
if (eqq1cd=. or eqq2cd=. or eqq3cd=. or eqq4cd=. or eqq5cd=.)
                then eq5d=.;
run;
```

STATISTICAL ANALYSIS PLAN

Title:	A phase 3 confirmatory study investigating the efficacy and safety of dupilumab Monotherapy administered to adult patients with moderate-to-severe atopic dermatitis
Protocol:	R668-AD-1334
Investigational product:	Dupilumab (REGN668)
Sponsor:	Regeneron Pharmaceuticals, Inc.
Statistician:	Haobo Ren, Ph.D.
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BAS	Biomarker analysis set
BSA	Body surface area
BUN	Blood urea nitrogen
CRF	Case report form
EAIR	The exposure-adjusted incidence rate
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonisation
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed effect model with repeated measures
NEPY	Number of events per 100 patient-years
NRS	Numerical rating scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic

PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PRC	Protocol review committee
PT	Preferred term
qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of this study. The SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for R668-AD-1334 study.

This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. These revisions will be based on blinded review of the study and data. This plan will be finalized prior to the final database lock.

1.1. Background and Rationale

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus, xerosis, and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD.

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction. Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption. Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated

application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation. Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids. Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

IL-4 and IL-13 have been implicated as an important inflammatory component. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents.

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. There has been no evidence in the phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab.

This is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable. This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021).

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

1.2.2. Secondary Objectives

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

1.3. Modifications from the Statistical Plan in the Final Protocol

Modifications from the Amended protocol 2 (final protocol) on Analyses of Secondary Efficacy Variables

- Multiple Imputation (MI) is used as the primary analysis method for continuous variables. MMRM will be used as a sensitivity analysis method for continuous variables. Sensitivity analysis by pattern mixture model will not be performed.
- Add the endpoints "Proportion of patients with improvement (reduction) of pruritus NRS ≥4 from baseline to week 16, to week 4 and to week 2, respectively" as key secondary endpoints
- Change the order of the hierarchy for the secondary endpoints, i.e. move the endpoint "Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16" prior to the endpoint of "Incidence of TESAEs from baseline through week 16"

Modifications from the Amended protocol 2 on concomitant medication/procedure

Any concomitant treatment is considered from the first dose of study medication in the SAP instead of the time of informed consent in the protocol

1.4. Modifications from the Previously Approved SAP

Item	Section	Changes/Updates Description	Rationale
1	2.1	Randomization strata: 'country' changed to 'region'	Correction
2	2.3	Removed the paragraph of ADA titer	Clarification
3	3.2	Updated the timing of PPS determination	Clarification
4	3.3	Added two analysis period for safety analysis	Clarification
5	3.4	Updated the description of PK analysis set	Clarification
6	4.1	Updated Demographic and baseline characteristics variables	Per clinical request
		Add the patient with inadequate response to	Per UK/Ireland HA

Item	Section	Changes/Updates Description	Rationale
		topicals (Yes/NO)	request
7	4.2	Updated the version of MedDRA	Clarification
8	4.4.2	Updated key and other efficacy endpoints	In response to FDA's comment
9	4.4.2	Updated introduction of HADS and POEM	Clarification
10	4.4.3	Updated introduction of EQ-5D and added some variables from section 4.8	Clarification
11	4.5.2	Removed the irrelevant description	Clarification
12	4.7	Updated introduction of ADA variables	Clarification
13	4.8	Updated introduction of ACQ-5, removed some variables other than biomarkers to section 4.4.3 and re-titled	Clarification
14	5.4	Added Number of patients who entered into follow-up period	Clarification
15	5.6	Updated the days cutoffs for the duration of treatment and duration of the observation period	Clarification
16	5.7	Updated the subgroup analyses	In response to comments from FDA and EMA
		Change the thread value for SCORAD subgroup	Per clinical request
17	5.7.2	Added WOCF to the sensitivity analyses	In response to FDA's comment
18	5.7.2	Updated the hierarchy of the secondary endpoints	Clarification
19	5.7.3	Updated the analysis of other efficacy endpoints	Clarification
20	5.8.1	Updated TEAE incidence	Per clinical request
21	5.8.1	Added NEPY, EAIR and associated analyses	Per clinical request
22	5.8.1	Added AESI	Per clinical request
23	5.10	Updated ADA algorithms	Clarification
24	5.11	Updated biomarker analyses	Clarification
25	6.1	Updated definition of baseline measurements	Clarification
26	6.3	Updated missing data handling rules	Clarification

Item	Section	Changes/Updates Description	Rationale
27	6.4	Updated analysis visit windowing algorithm	Clarification
28	10.5	Added AESI search criteria	In response to FDA's comments

2. INVESTIGATIONAL PLAN

2.1. Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study duration is between 16 weeks (16-week treatment period) and 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study. Eligible patients will be randomized in a 1:1:1 ratio to qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by regions (Asia Pacific, East Europe, North and South America and West Europe).

2.2. Sample Size and Power Considerations

To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size was increased to 600 in total with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment, respectively). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. Power calculation was implemented by nQuery Advisor 7.0.

Additional power calculation based on the secondary endpoint "proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16": As the analysis includes patients with baseline peak pruritus NRS ≥4, assumed that 180 such patients are randomized into each treatment group, with responder rates 39% and 9% for dupilumab and placebo respectively, the analysis can provide 99% power at 0.025 level from each comparison.

2.3. Study Plan

The study consists of a screening period, a treatment period and a follow-up period as presented below:

Screening	**Treatment Period** [1,2]			**Follow-Up**[3]
V1	V2	V3 to V17 (qw)	V18	V19 to V21 (q4w)
	Baseline	W1 to W15	End of Treatment[3]	End of Study
(Day –35 to Day -1)	(Day 1)	(Day 8 to Day 106)	(Day 113)	(Day 141 to Day 197)

[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered.

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out. Patients may be re-screened 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 at least twice daily for at least the 7 consecutive days immediately before randomization and continue throughout the study. To allow adequate assessment of skin dryness, moisturizers should not be applied on the areas of non-lesional skin used for such assessments for at least 8 hours before the clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab

concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Section 10.2). ADA samples collected at day 1 (baseline) at Week 16 (EOT), at Week 28 (EOS), and at early termination (ET) will be analyzed for ADA. In response to AE's of special interest like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgement of the medical investigator and/or medical monitor.

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in the maintenance study, R668-AD-1415. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study (R668-AD-1225), but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations of analysis will be used for all statistical analyses.

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). This is the primary analysis population for efficacy analyses.

Patient who was randomized more than once will be analyzed as distinct patients based on the treatment allocated at the initial randomization and will be analyzed separately.

Patients who temporarily or 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 and complete all study assessments per the study schedule.

3.2. Per Protocol Analysis Set

The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations.

A major efficacy-related protocol violation is one that may affect the interpretation of study efficacy results. The criteria of major efficacy-related protocol deviation are defined as following:

- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
  - Inclusion criteria 3, 4, 5 and 6
  - Exclusion criteria 3 ,4, 5, 6, 7 and 8
- Patients who received <80% or >120% of the scheduled doses during the study treatment period

Final determination of the PPS will be made in the blinded manner prior to the database lock.

3.3. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive any study drug, and will be analyzed as treated.

The actual treatment group is defined by the following rules:

- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen
- For patients on dupilumab accidentally receiving ≤ 2 injections different from the planned treatment, the actual treatment group allocation for as-treated analysis will be the planned dupilumab dose / regimen
- For patients on dupilumab receiving > 2 injections different from planned treatment, the actual treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized

The safety analyses will be based on the SAF.

For safety summaries, three analysis periods are defined as follows:

- Week 16 treatment period is defined as
  - Day 1 to the study completion date of the week 16 visit (113 days starting from the first dose of study drug if the date of the week 16 treatment visit is

unavailable) for those patients who entered the maintenance study (R668-AD-1415) which is defined as having the "Transition into another study R668-AD-1415 SOLO-CONTINUE study" on the CRF Study Completion Status page checked

- Day 1 to the week 16 visit date or early termination date, whichever comes first, for those patients who did not enter the maintenance study (R668-AD-1415)

- Follow-up period is defined as the date after the week 16 visit date (113 days starting from the first dose of study drug if the date of Week 16 treatment visit is unavailable) to the date of the end of study visit
- Overall study Period is defined as day 1 to the date of the end of study visit, consisting of both the treatment and follow-up periods

The SAF will be the basis for the analyses for the week 16 treatment period and overall study period; however, for the analyses for the follow-up period, only a subset of SAF will be included, which is defined as the patients who entered the follow-up period and had at least one visit after week 16 treatment visit.

3.4. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set includes all randomized patients who received any study drug and who had at least one qualified PK sample result following the first dose of study drug up to Week 16, and will be analyzed as the treated groups defined in the SAF.

The PKAS will be applied for the PK analysis according to the separately documented PK analysis plan.

3.5. The ADA Analysis Set (AAS)

The ADA population will consist of all treated patients who received any study drug and who had at least one reportable ADA result (either “ADA negative” or “ADA positive”) after first dose of the study drug.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age at screening with grouping (year; ≥18-<40, ≥40-<65, ≥65), Sex, Ethnicity with grouping (Hispanic or Latino, Not-Hispanic or Latino), Race with grouping (White, Black, Asian, Other), Region (for global submission: Americas, Asia Pacific, East Europe, West Europe; for Japan submission: Japan, Rest of world), Country, Baseline weight with grouping (kg, <70; ≥70-<100, ≥100), Height (m), and BMI (kg/m^2; <15, ≥15-<25, ≥25-<30, ≥30), Patients with inadequate response to topicals (Yes/No) with the reasons for patients who are “No” for inadequate response to topicals

- Baseline characteristics: Duration of AD disease with grouping (year; <26, ≥26 years), Pruritus numerical rating scale (NRS) for maximum or average itch intensity, Pruritus categorical scale, Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, Global Individual Signs Score (GISS), SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) Involvement of Atopic Dermatitis, Patient global assessment of disease status, Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), EQ-5D and Hospital Anxiety and Depression Scale (HADS)

4.2. Medical History and Atopic Disease Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA (18.0 at the time of BLA submission) at the coding CRO. Information on conditions related to AD includes diagnosis of AD and AD treatment history, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy hives and other allergies due to medications, animals, plants, mold, dust mites, etc. Recent AD history within 1 year before the screening visit is also collected with information of number of AD flares and episodes of skin infections requiring pharmacological treatment.

4.3. Pre-treatment/ Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the EOS visit.

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

Prohibited concomitant medications/procedures during the study

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

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with TCS or TCI

- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

Rescue treatments for AD: If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator.

Patients who receive rescue treatment during the study treatment period will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment.

If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) study treatment will be immediately discontinued.

After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure. A predetermined algorithm for rescue medications listed in Section 10.6 will be used to programmatically search the concomitant medications (CMs). The rescue CMs will be reviewed and adjudicated by the medical monitor in a blinded fashion. Similarly, the rescue procedures will also be manually adjudicated by the medical monitor based on the concomitant procedure data.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variable

During discussions with health authorities, different health authorities requested different primary endpoints, although the conduct of the study will be the same for all countries. As a result, the primary endpoint for US and US reference market countries is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Union (EU) and EU reference market countries, as well as Japan, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument to rate AD disease severity globally in clinical studies. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration. IGA score will be assessed at every scheduled and unscheduled clinic visit.

Eczema Area and Severity Index (EASI)

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 score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section.

The EASI will be collected at every scheduled and unscheduled clinic visit.

4.4.2. Secondary Efficacy Variables

The key secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA EU and EU reference market countries, as well as Japan as it is already a co-primary endpoint)

- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 4
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 2

Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average itches 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 overall (on average) during the previous 24 hours?"
- For maximum itches 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

If there are multiple NRS to the same question (average or maximum itch intensity) collected on the same day, average of all the scores collected will be taken.

The baseline NRS is defined as the prorated average of the NRSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline NRS, The mean weekly NRS is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3. The baseline NRS and mean weekly NRS will be calculated for average itch intensity and peak itch intensity separately.

Other secondary efficacy endpoints are:

- Change from baseline to week 16 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to week 16
- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16

- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Percent change from baseline to week 2 in weekly average of peak daily pruritus NRS
- Change in ACQ-5 score from baseline to week 16
- Change in SNOT-22 score from baseline to week 16
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16. The skin infection TEAEs will be identified based on blinded adjudication of all reported TEAEs under these two primary system organ classes (SOCs): SOC = "infection and infestations" or SOC = "Skin and subcutaneous tissue disorders". Blinded adjudication will be done and finalized by the study medical monitor before database lock.
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16

Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 every scheduled and unscheduled clinic visit.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). The extent of AD is assessed by the Investigator as a percentage of each defined body area 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 (erythema, oedema / papulation, excoriations, lichenification, oozing / crusts and dryness) of AD is assessed by the Investigator 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 (VAS), 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. The maximum SCORAD score is 103.

Patients will undergo this assessment at every scheduled and unscheduled clinic visit.

Global Individual Signs Score (GISS)

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally by the Investigator (i.e., each assessed for the whole body, not by anatomical region) on a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe) using the EASI severity grading criteria. The cumulative score is the sum of the four components, which will be ranged from 0 to 12. The GISS will be assessed at every scheduled and unscheduled clinic visit.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire (Badia 1999) used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on Quality of Life (QoL). The format is a simple response to 10 items, which assess QoL over the past week. For each item, the scale is rated as follows: 0='not at all'='not relevant'; 1='a little'; 2='a lot'; 3='very much'='yes' in question 7, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. For general inflammatory skin conditions a change in DLQI score of at least 4 points is considered clinically important (Basra 2015).The DLQI will be assessed at every scheduled and unscheduled clinic visit.

Handling missing items from DLQI:

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
ii. If two or more questions are left unanswered the questionnaire is not scored.
iii. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
iv. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
v. If two or more response options are ticked for one question, the response option with the highest score should be recorded.
vi. The DLQI can be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

Hospital Anxiety and Depression Scale (HADS)

The HADS is a Likert-scale tool widely used to detect states of anxiety and depression in a general hospital setting (Bjelland 2002). The 14 items on the questionnaire, assessing how the patient has been feeling in the past week, include 7 items that are related to anxiety (odd numbered questions) and 7 items that are related to depression (even numbered questions). Questions 2, 4, 7, 9, 12, and 14 are scored from 0 (less distress) to 3 (greater distress) according to the content of the item. Questions 1, 3, 5, 6, 8, 10, 11, and 13 are reverse scored from 0 (greater distress) to 3 (less distress). A person can score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8–10 represents 'probable case' and 0–7 'not a case' (Zigmond 1983).

For each sub-scale: if one question is missing, the response will be imputed as the mean of the remaining six questions. If more than one question is missing, then the subscale is set to missing. The total score is the sum of the two sub-scores.

HADS will be assessed at every scheduled and unscheduled clinic visit.

Patient Oriented Eczema Measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with atopic eczema (Charman 2004). The format is patient response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week and each item is a 5-point scale (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4 days', 3 = '5 to 6' days, and 4 = 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28 and reflects disease-related morbidity; a high score is indicative of a poor QOL.

The following POEM banding scores have been established (Charman 2004): 0 to 2 = Clear or almost clear; 3 to 7 = Mild eczema; 8 to 16 = Moderate eczema; 17 to 24 = Severe eczema; 25 to 28 = Very severe eczema. If two or more response options are selected for a question, then the response option with the highest score is recorded. If one question of the seven is left unanswered, then that question is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28.

If two or more questions are left unanswered, then the questionnaire is not scored and is set to missing.

The POEM will be assessed at every scheduled and unscheduled clinic visit.

DLQI, HADS and POEM will be administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

4.4.3. Other Efficacy Variables

Other efficacy variables include:

- Change and percent change from baseline to week 16 in EQ-5D
- Proportion of patients who respond "absence of pruritus" or "mild pruritus" in PCS at week 16

- Proportion of patients who respond "very good" or "excellent in Patient Global Assessment of Disease Status at week 16
- Proportion of patients who respond "very good" or "excellent in Patient Global Assessment of Treatment Effect at week 16
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Sick Leave/Missed School Days Assessment

Pruritus Categorical Scale (PCS)

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in clinical studies of AD and has less of a "middling" effect (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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

For each day, if there are multiple PCS scores collected on the same day, the maximum (worst) of all the scores collected will be chosen. For each week, calculate round prorated average of collected scores for Category Score. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3 round to 1.0.

The baseline PCS is defined as the round prorated average of the PCSs reported continuously for 7 days right before the baseline visit.

Patient Global Assessment of Disease Status

Patients will rate their overall wellbeing based on a 5-point Likert scale. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing". Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5). Patients will undergo this assessment at the following visits: screening, day 1/baseline (pre-dose), and days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

Patient Global Assessment of Treatment Effect

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5). Patients will undergo this assessment at the following visits: days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

EQ-5D

The EuroQoL 5-Dimension Health Questionnaire 3 Level (EQ-5D-3L) is a standardized measure of health status developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economic appraisal (Greiner 2005). The EQ-5D-3L is a self-administered questionnaire used to assess health status 'today' that is divided into two sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3).

A composite health index is then defined by combining the levels for each of the 5 dimensions, potentially producing 243 different states. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health." Values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model and weighted according to the social preferences of the UK population. The minimum value for the single index utility score is –0.594.

The second section of the questionnaire, the EuroQol Visual Analogue Scale (EQVAS), measures self-rated (global) health status in terms of a visual analogue scale where 100 represents the best possible health state and 0 represents the worst possible health state. EQ-5D-3L self-reported VAS data generates information on the self-perceived overall health-related quality of life. Section 10.4 provides the SAS code to derive the index utility score using UK based population.

EQ-5D-3L will be assessed at every scheduled and unscheduled clinic visit and administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

Juniper Asthma Control Questionnaire (ACQ-5)

The 5-question (symptoms only) version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of asthma and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment). A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ, any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as

missing. If only one question has missing value, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

Sinonasal Outcome Test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

It contains 22 items. The total score of the SNOT-22 is calculated by summation of all the item scores. The total score ranges from 0 to 110. The MCID is equal to 8.9. For patients where some SNOT-22 items were incomplete, a total score for the SNOT-22 will be imputed as mean of the completed items, providing at least 50% of items have been completed. If more than 50% of items are missing, the total score will be considered as missing.

Twenty two items are classified into five domains as in following table. The score for each domain is the sum of response to each question in that domain. Domain score will be imputed as mean of the completed items in that domain, providing at least 50% of items in that domain have been completed.

Domain	Items
Nasal	2, 3, 4, 6, 7, 12
Ear	8, 9, 10
Sleep	13, 14, 15, 16
General and practical	1, 5, 11, 17, 18, 19
Emotional	20, 21, 22

Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at day 1/baseline, days 29, 57, 85, 113, 141, 169, 197 (EOS), unscheduled visits and ET.

4.5. Safety Variables

4.5.1. Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term", "High Level Term" and the associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0 at the time of BLA submission).

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal (investigational) product.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

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

The pre-treatment period is defined as the period from the subject providing informed consent up to the first dose of study drug. The treatment and follow-up period is defined as the period from the administration of first study dose to the EOS visit.

The pre-treatment AE and treatment emergent AE (TEAE) is defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during pre-treatment period.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered as TEAEs.

4.5.2. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Blood samples for serum chemistry and hematology testing will be collected at screening (day -35 to day -1), baseline (day 1), on days 29, 57, 85, 113, 197 (EOS) or ET, and at unscheduled visits. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population.

Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory.

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[1]

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be reflexly measured when CPK >5X the ULN

Hematology with Differential

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

Urinalysis

Urine samples for urinalysis will be collected to measure overall patient health at screening, and will also be collected at (day -28 to day -1), baseline (day 1), on days 113, 197 (EOS) or ET, and at unscheduled visits.

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

4.5.3. Vital Sign Variables

The following vital signs parameters will be collected:

- Weight (kg) and height (cm)
- Respiratory rate (bpm)
- Heart rate (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (^{o}C)

Weight is determined at screening and day 1/baseline, and days 113, 197 (EOS), any unscheduled visit, or ET. Height is only measure at screening. Other vital signs are collected pre-dose at every scheduled and unscheduled clinic visit. In addition, blood pressure and heart rate will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation. If there are multiple measurements within the time window, the last value will be included.

4.5.4. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] =QT/[$RR^{0.33}$] and QTc Bazett [QTcB]=QT/[$RR^{0.5}$]) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at screening, days 113 and 197 (EOS) or ET.

4.5.5. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.

A thorough and complete physical examination will be performed at screening, day 113, and day 197 (EOS) or ET.

4.6. Pharmacokinetic (PK) Variables

This section provides the outline of the PK variables for the study and details of PK variables will be describe separately in PK analysis plans

- Characterization of functional dupilumab concentrations in through week 16
- Correlation analyses:
  - Body weight vs functional dupilumab concentrations
  - Functional dupilumab concentrations vs clinical outcomes

Samples for drug concentration will be collected at day 1/baseline (pre-dose), days 15, 29, 57, 85, 113, 197 (EOS), unscheduled visits and ET. Pharmacokinetic variables may include but not limited to C_{trough} over time, $C_{last,}$ $T_{last,}$ time to steady state and $C_{troughSS}$ (steady state trough concentration).

4.7. Antibody (ADA) Variable

The variables include ADA status (positive or negative) and titer as follows:

- Total subjects negative in the ADA assay at all time points analyzed
- Total subjects positive in the ADA assay at any time point analyzed
- Total subjects with preexisting immunoreactivity
- Pre-existing immunoreactivity- defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response

at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels.

- Total subjects with treatment emergent response is 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 as Persistent, Indeterminate or Transient
  - Persistent Response - Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12- week period (greater than 85 days), with no ADA negative samples or any missing sample in between.
  - Indeterminate Response - as a treatment-emergent response with only the last collected sample positive in the ADA assay
  - Transient Response - a treatment emergent ADA positive assay response that is not considered persistent or indeterminate.
- Total subjects with treatment boosted response
- 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 Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

ADA positive samples will be further characterized for the strength of the ADA response by assessment of ADA titers and for the presence of neutralizing antibody (NAb) response.

4.8. Biomarkers

Biomarkers to be analyzed in this study are:

- TARC and total serum IgE
- antigen-specific IgE
- hs-CRP, ANA, anti dsDNA, anti-TPO

TARC and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs in circulation, indicating they are atopic. To further understand atopy in this patient population, region-specific, allergen-specific IgE panels will be performed.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti-dsDNA, anti-TPO, and ANA) will be measured.

Samples will be collected at time points according to the schedule in Section 10.2.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

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

5.1. Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups based on FAS. Listing of demographics and baseline characteristics will be presented.

5.2. Medical and AD History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

Medical history will be listed, sorted by treatment groups based on the SAF.

5.3. Pre-treatment/Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications, prohibited medications/procedures and rescue medications/procedures will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined dupilumab treatment groups.

The procedure will be summarized by treatment group to MedDRA 18.0 at the time of BLA submission by system organ class (SOC) and preferred term (PT) and sorted by decreasing frequency of SOC and PT, based on the overall incidence for combined dupilumab treatment groups.

Listing of pre-treatment medication and concomitant medications will include generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, route.

The detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized by topical and systemic groups. Kaplan Meier curves for time to first rescue use will be generated.

The compliance of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group.

5.4. Subject Disposition

The following summaries by table will be provided:

- The total number of screened patients
- 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 treatment and the reasons for the discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation
- Number of patients who entered into follow-up period

The following listings will be provided:

- Listing of subject disposition including: date of randomization, date of the last visit, received dose, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized, including the patients who missed active study drug doses to the point that their cumulative exposure ends up being closer to another study regimen that is different from the one to which they had been randomized (e.g., a patient randomized to 300 mg qw who missed 30-50% of doses will be closer to 300 mg q2w than to the originally assigned 300 mg qw)
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation, summary tables of reasons will be provided
- Summary table with listing of protocol deviations will be provided

5.5. Dose Administration

The compliance with protocol-defined investigational product will be calculated as follows:

Treatment Compliance= (Number of injections during exposure period) / (Number of planned injections during exposure period) x 100%

Loading doses for the same patient will be counted as 1.

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80% and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information and whether or not the total dose is administered for each dose will be presented.

If subjects received treatment different from the randomized treatment or stopped treatment due to an AE, or overdosed, the listings will be provided.

5.6. Treatment Exposure and Observation Period

The duration of treatment exposure period during the study is calculated as:

(Date of last study drug injection – date of first study drug injection) + 7

Note: exposure will be calculated based on the last study drug injection date and first study drug injection date regardless of temporary dosing interruption.

The duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well:

≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days, ≥98 days, ≥112 days, ≥126 days, ≥140 days, ≥154 days, ≥168 days, ≥182 days, ≥196 days.

The duration of observation period during the study is calculated as:

[Date of the last study visit – date of the first study injection] +1.

The duration of observation period will be summarized descriptively as a quantitative data (n, mean, SD, median, minimum and maximum). In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest is specified as:

≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 43 days, ≥50 days, ≥ 57 days, ≥ 64 days, ≥ 71 days, ≥ 78 days, ≥ 85 days, ≥99 days, ≥113 days, ≥127 days, ≥141 days, ≥155 days, ≥169 days, ≥183 days, ≥197 days.

5.7. Analyses of Efficacy Variables

For all efficacy variables, the analysis will be comparisons of each dupilumab regimen and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested for each dupilumab regimen group and the placebo group:

H0: $p_{dupilumab} = p_{placebo}$, where p stands for the proportion of responders in a treatment group

H1: $p_{dupilumab} \neq p_{placebo}$.

The analyses of efficacy variables are described in the subsections below and summarized in Section 10.1.

Subgroups are defined by key baseline factors recorded on the CRF and listed to be considered for primary and secondary efficacy analyses:

- Age group (≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black, Asian, Other)

- Duration of AD (< 26 years, ≥26 years)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)
- BMI (<15, ≥15-<25, ≥25-<30, ≥30
- Region for global submission (Asia Pacific, Eastern Europe, North and South America, Western Europe)
- Region for Japan submission (Japan, Rest of world)
- Baseline disease severity [moderate (IGA=3) and severe (IGA=4)]
- Baseline moderated-to-severe EASI (<20, ≥20)
- Baseline severe EASI (<25, ≥25)
- Baseline peak NRS (<7, ≥7)
- Baseline Body Surface Area (BSA) (≥10%-<30%, ≥30%-<50%, ≥50%)
- Baseline SCORAD score (≤ 50, >50)
- Previous use of systemic immunosuppressants for AD (Yes, No)
- Previous use of systemic cyclosporine for AD (Yes, No)
- Previous usage of Azathioprine (Aza) (Yes, No)
- Previous usage of Methotrexate (MTX) (Yes, No)
- History of asthma (Yes, No)
- History of nasal polys (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergies (Yes, No)

5.7.1. Analysis of Primary Efficacy Variables

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

Handling of dropouts or adjudicated rescue medication or missing value for the binary response variables as the primary analysis

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

To account for the impact of rescue medication on the efficacy effect:

For the binary efficacy endpoints, if rescue medication is used (see Section 4.3 or rescue), the patient will be specified as a non-responder from the time the rescue is used.

If the patient has the missing value at week 16, then it will be counted as a non-responder at week 16.

Sensitivity analyses

1. Post-baseline Last Observation Carried Forward (LOCF) approach after censoring for rescue medication use or study withdrawal 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.
2. All observed data, no matter if rescue medication is used or data is collected after study withdrawal, will be included for the primary endpoint. Patients with missing value will be counted as non-responder.
3. All observed data, no matter if rescue treatment is used or data is collected after study withdrawal, will be included for the primary endpoint (regardless of rescue medication used), missing data will not be imputed as non-responder.

The primary efficacy analyses will be performed on FAS, as well as on PPS as a supporting analysis.

5.7.2. Analyses of Secondary Efficacy Variables

The binary secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoints.

The endpoint "Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16" will only be analyzed for patients with baseline peak pruritus NRS ≥4.

The continuous endpoints will be analyzed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model as the primary analysis for continuous variables. Patients' efficacy data through week 16 after the rescue medication usage will be set to missing first, and then be imputed by the multiple imputation method. Missing data from the FAS will be imputed 50 times to generate 50 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. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.
>
> Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, randomization strata (region, disease severity), and relevant baseline.

The week 16 data of each of the 50 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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 50 analyses using Rubin's formula.

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, the baseline value and the randomization strata
- Measured endpoint values from every clinic visit up to week 16

Categorical variables included in above model (i.e., treatment group and randomization strata) are not expected to be missing.

To account for the impact of rescue medication on the efficacy effect:

- Continuous efficacy endpoints: if a patient receives rescue medication that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue medication is initiated will be treated as missing.

Sensitivity analyses

In addition to the MI method described previously, sensitivity analyses for the continuous endpoints for EASI and/or Pruritus NRS will be conducted as described below:

1. The sensitivity analysis based on all observed data no matter if rescue medication is used or data is collected after withdrawal using MI method will be performed.
2. This sensitivity analysis will use a mixed-effect model repeated measures (MMRM). The model will include factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within-patient errors. Denominator degrees of freedom will be estimated using approximation of SATTERTH. The efficacy data will be set to missing after rescue medication is used. Afterwards no imputation will be made.
3. The MMRM model will provide least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error, confidence interval, and the p-value for treatment comparisons. The graph of LS-mean +/- se by visit will be provided.
4. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue medication is used. The post-baseline LOCF method will then be used to impute missing values.
5. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue medication is used. The post-baseline worst-observed-case-forward (WOCF) method will then be used to impute missing values.
6. This sensitivity analysis will use ANCOVA model, including study, the treatment group, the baseline value and the randomization strata. The efficacy data will be based on all observed value regardless rescue medication used. No imputation method will be applied for the sensitivity analysis.

Analysis of incidence of TEAE-related variables

- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16

These endpoints will be analyzed for patient in SAF. The week 16 treatment period is defined in Section 3.3. The Cochran-Mantel-Haenszel test adjusted for randomization strata (region, disease severity) will be used for the percentage of patients with events described above through week 16.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and placebo will be derived by testing each active dose group versus placebo separately. Two-sided 95% confidence intervals of the rate ratio will be provided. The estimated events rate and its 2-sided confidence intervals will be provided for each treatment group.

Multiplicity Considerations

For US and US reference market countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the previous one.

For EU and EU reference market countries, as well as Japan:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16

- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 4
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 2
- Change from baseline to week 16 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to week 16
- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Percent change from baseline to week 2 in weekly average of peak daily pruritus NRS
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

5.7.3. Analyses of Other Efficacy Variables

Analyses of categorical variables will be similar to the primary analysis; analyses of continuous variables similar to the secondary analyses.

Changes from baseline to each measurement visit in ACQ-5 and SNOT-22 will be summarized by treatment group and visit. Number of sick Leave/missed school days from each assessment will be summarized by treatment group.

5.8. Analysis of Safety Data

The summary of safety and tolerance will be performed based on SAF.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs, and 12-lead ECG.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables, vital signs and ECG are defined in Section 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

Subgroups are defined by key baseline factors recorded on the CRF and listed to be considered for safety analyses:

- Age group (≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black, Asian, Other)
- Duration of AD (< 26 years, ≥26 years)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)
- Region for Japan submission (Japan, Rest of world)

5.8.1. Analysis of Adverse Events

The number and proportion of patients will be summarized separately for the week 16 treatment period, the follow-up period and overall study period, described in Section 3.3. Adverse event (AE) incidence tables will be presented for each treatment group along with total of dupilumab doses as well as for selected subgroups, including the number (n) and percentage (%) of patients experiencing an AE, where multiple instances of the same event occur in the same patient the event will be counted only once for that patient, at the first dose level in which it occurs (when applicable). The denominator for computation of percentages is the number of patients in each treatment group, across all dupilumab regimens.

The number and proportion of patients reporting TEAEs will be summarized, sorted by decreasing frequency of SOC and PT for the highest dupilumab dose. The number and proportions of patients reporting TEAEs will also be summarized, sorted by decreasing frequency of SOC, HLT and PT for the highest dupilumab dose.

Patient listings will be provided for all SAEs, death, and TEAEs leading to permanent treatment discontinuation.

The following variables will be included in the listing:

- Patient ID
- Treatment group
- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)
- Verbatim Term
- AE start date and end date/ongoing (using both calendar days and study days)
- AE Duration
- Relationship of AE to study drug: unrelated or related
- Action taken: Dose withdrawn temporarily, Dose reduced, Dose withdrawn permanently, Dose not changed, Not known or Not applicable
- Severity: using a 3–point scale (mild, moderate, or severe)
- Treatment: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with sequelae, recovering/ resolving, not recovered/not resolved, fatal or unknown

In addition, to account for potentially differential exposure time, two types of exposure-adjusted analyses will be provided, namely, Number of Events per 100 Patient-Year (NEPY) and Number of patients with at least one event per 100 patient-years. These calculations will be adjusted for dose exposure for the Week 16 treatment period and for the entire study period.

Number of events per 100 patient-years (NEPY)

The NEPY will be calculated as the number of events occurring in the population divided by the sum of the exposure over all patients (i.e., total exposure) in the TEAE period.

$$NEPY = 100 \times \frac{\sum n_i}{\sum T_i}$$

where n_i is the number of events observed for patient i; T_i is total TEAE exposure for patient i in person-year unit.

Number of patients with at least one event per 100 patient-years

The exposure-adjusted incidence rate (EAIR) can be defined as the number of patients with at least one specific adverse event per 100 patients taking the treatment for 1 year (52 weeks). The number of patients with at least one event per 100 patient-years will be calculated as the number of patients having a specific event divided by the total person-year and at risk of an initial occurrence of the event. In particular, the EAIR is computed as follows:

$$EAIR = 100 \times \frac{n}{\sum t_i}$$

where n is the number of patients with the specific adverse event; it is a patient's exposure time in person-year unit. For each of the adverse events of interest, the exposure time t_i for patients who have experienced the adverse experience will be defined as the time to first adverse experience, whereas the exposure time for those who have not had this adverse experience will be total duration of exposure in the TEAE period.

The time to first AESIs (TEAE by category) or TEAE leading to permanent treatment discontinuation will be assessed by Kaplan-Meier estimates (K-M plot). In order to detect any safety signals, the hazard ratio (HR) will be provided together with the corresponding 95% confidence interval (CI) for the selected adverse events during the 16 week treatment period. Hazard ratios will be calculated using a Cox model including factors of treatment group, and randomization strata. The time is defined as the date of first event – the date of first dose + 1. Patients without an event will be censored at the end of 16-week treatment period. Graphs of cumulative incidence rate over time will be presented by treatment group.

Overall TEAE summary

The overall summary of TEAEs will be provided with number and proportions of patients with any:

- TEAE
- TEAE related to study drug
- Serious TEAE
- TEAE of special interest (AESI)/TEAE by syndrome
- TEAE leading to death
- TEAE leading to permanent treatment discontinuation
- TEAEs leading to temporary treatment discontinuation by SOC and PT

AESI/TEAE by syndrome:

- Anaphylactic reactions
- Acute allergic reaction
- Severe injection site reactions that last longer than 24 hours
- Mycosis fungoides
- Cutaneous T-cell dyscrasia
- Any severe infection
- Any infection requiring treatment with parenteral antibiotics
- Any infection requiring treatment with oral antibiotics/anti-viral/anti-fungal for longer than 2 weeks
- Any clinical endoparasitisis
- Any opportunistic infection
- Suicidal behavior

Section 10.5 provides a list of AESIs search criteria.

TEAE Incidence

Number and proportions of patients reporting TEAEs will be summarized for the following TEAEs:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - TEAEs by SOC/HLT/PT with HLT ≥5% in any treatment groups
  - TEAEs by SOC/HLT/PT with PT ≥5% in any treatment groups
  - TEAEs by SOC/PT with PT ≥5% in any treatment groups
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - Severe TEAEs by SOC/HLT/PT
  - TEAEs related to study medication as assessed by the investigator by SOC/PT
  - Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
  - TEAE of special interest/TEAE by category
- Serious TEAEs:
  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLT/PT
  - Serious TEAEs related to study medication as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- TEAEs leading to temporary discontinuation of study treatment by SOC/PT
- Death by SOC/PT

Exposure-adjusted TEAE Incidence Rates (in patient-years)

The number of patients with event per 100 patient-year will be summarized in the week 16 treatment period and follow-up period and the overall period:

- TEAEs by SOC and PT
- Severe TEAEs by SOC/PT
- TEAEs related to study medication as assessed by the investigator by SOC/PT

- Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
- Serious TEAEs by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- TEAEs leading to temporary discontinuation of study treatment by SOC/PT

Number and proportions of subjects reporting TEAEs listed above will be summarized, sorted by decreasing frequency of SOC and PT for the highest dose level.

Summaries of TEAEs will include:

- Proportion of subjects with at least one TEAEs
- Proportions of subjects with at least one TEAEs by SOC/PT
- Proportions of subjects with at least one TEAEs by SOC/HLT/PT
- Proportions of subjects with at least one TEAEs by PT
- Proportion of subjects with at least one TEAEs by severity by SOC/PT
- Proportion of subjects with at least one TEAEs related to study medication by SOC/PT
- Proportion of subjects with at least one serious TEAEs by SOC/PT
- Proportion of subjects with TEAEs leading to discontinuation of study treatment by SOC/PT

Summary of the most frequent (≥5%) TEAEs by SOC, HLT, PT, respectively, in the aggregate dupilumab groups and in the overall study population will be provided.

SAEs/AESI during the Week 16 treatment period, follow-up period and overall period will be listed.

5.8.2. Analysis of Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with abnormal lab value during study whose screening and baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs during study, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by subject and visit will be provided.

5.8.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings will be provided with flags indicating the treatment-emergent PCSVs, depending on data.

5.8.4. Analysis of Physical Exams

The number (n) and percentage (%) of subjects with abnormal physical exams will be summarized at baseline, end of treatment period and end of study by treatment group. A summary of treatment-emergent abnormal findings will be provided.

5.8.5. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings will be provided with flags indicating PCSVs, depending on data.

5.9. Analysis of Pharmacokinetic Data

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

5.10. Analysis of ADA Data

The ADA variables described in Section 4.7 will be summarized using descriptive statistics by dose cohorts in the ADA analysis set. Frequency tables of the proportion of patients developing ADA positivity in the ADA assay, Neutralizing antibody status in the NAb assay, pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent, indeterminate and transient ADA responses and titers will be presented as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Listing of all ADA peak titer levels and neutralizing antibody status will be provided for ADA positive subjects.

The following summaries will be performed on the AAS:

- Number (%) of patients ADA positive at any time at time points analyzed by treatment group
- ADA peak titers using descriptive statistics (median, minimum and maximum) by treatment group
- ADA titers using descriptive statistics (median, minimum and maximum) by treatment group and ADA assessment time point indicated in Section 10.2
- Number (%) of patients with NAb status (negative or positive) by treatment group
- Number (%) of patients with pre-existing ADA, treatment-emergent ADA, and treatment boosted ADA response by treatment group
- Number (%) of patients with persistent, transient and indeterminate treatment-emergent ADA response by treatment group

Correlations between ADA variables (e.g. ADA peak titers, neutralizing antibody status, treatment-emergent, treatment-boosted, transient, indeterminate and persistent ADA responses) and PK may also be explored (e.g, scatter plot) and the detailed analysis will be described separately in the PK analysis report.

Impact of ADA on Safety and Efficacy

Correlation analysis of safety versus ADA positive status and neutralizing antibody status may be performed in SAF.

The safety assessment will focus on the following events:

- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Number (%) of patients with the above mentioned safety events will be summarized by ADA status (positive or negative), and presence of neutralizing antibody (positive or negative) during the TEAE period.

In addition, the primary endpoint and key secondary efficacy endpoints will be summarized in patients with and without ADA (positive vs. negative) and neutralizing antibody (positive or negative) status if applicable.

5.11. Analysis of Biomarkers

Descriptive statistics for the observed value, change and percent change from baseline value by treatment and visit will be provided for the following biomarker variables:

- TARC (screening, days 1, 15, 29, 57, 85, 113, 197)
- total serum IgE (screening, days 1, 29, 57, 85, 113, 141, 169, 197)
- antigen-specific IgE (screening, days 1, 29, 57, 85, 113, 197)
- hs-CRP (screening, days 1, 57, 85, 113, 197)

Proportions for the following binary biomarkers will be reported:

- ANA, anti dsDNA, anti-TPO (screening, days 1, 57, 85, 113, 197)

The Wilcoxon signed-rank test stratified by the baseline disease severity will be used to test if the change or percentage change from baseline value is significantly different from zero. P-value will be reported.

Exploratory analyses for the difference between dupilumab groups and placebo on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group and the baseline disease severity as fixed effects, and the relevant baseline values as covariate. Missing value will be imputed by LOCF method for visits between post-baseline to visit 18 (week 16). After visit 18, no imputation will be made. P-value for difference from placebo will be provided.

Correlation of baseline TARC (measured value) and IgE (measured value) with the following clinical endpoints will be explored using the Spearman's rho test. Both Spearman correlation coefficients and p-value will be reported.

- Percent change from baseline to week 16 in EASI score
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD

Association of baseline TARC (measured value) and IgE (measured value) with the following clinical endpoints will be explored using the ANOVA model. The model will include the baseline biomarker value as the dependent variable, and the responder/non-responder from the endpoint, the baseline disease severity and the treatment group as the categorical factor. P-value will be provided to show significance of the responder/non-responder factor.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of peak daily pruritus NRS $\geq$3 from baseline to week 16

Association of positivity to at least one antigen-specific IgE with the following clinical endpoints will be explored using CMH test stratified by the baseline disease severity. The risk ratio and p-value from the chisq test will be provided.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of peak daily pruritus NRS $\geq$3 from baseline to week 16

Correlation/association will be implemented on the Placebo, dup 300 mg Q2W, dup 300 mg QW and combined dupilumab (dup 300 mg Q2W and QW) groups, respectively.

Shift tables from baselines status to post-baseline status by visit and by phases of treatment period and whole observation period until EoS will be provided for hs-CRP, ANA, anti dsDNA and anti-TPO variables will be provided by treatment group. The standard line plots (means +/- se) for continuous variables will be provided.

All above analyses will be performed on the FAS for:

- All observed data, no matter if rescue medication is used or data is collected after study withdrawal
- All observed data with censoring after rescue medication use or study withdrawal.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of NRS is defined in Section 4.4.2. The following rules specify the determination by both date/time information:

1. For the AE, lab (including biomarker), PK and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.
2. For other data except AE, lab (including biomarker), PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen- failure subject ID or enrolled subject ID.

6.2. General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAE. For example, if the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as "related" in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to align with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use the last visit study date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of last study visit date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.4. Analysis Visit Window

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG, ADA) will be summarized by the study scheduled visits described Section 10.2, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT/EOS visits, based on the study day:

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 1	8	[2,11]
4	Week 2	15	[12,18]
5	Week 3	22	[19, 25]
6	Week 4	29	[26, 32]
7	Week 5	36	[33, 39]
8	Week 6	43	[40, 46]
9	Week7	50	[47, 53]
10	Week 8	57	[54, 60]
11	Week 9	64	[61, 67]
12	Week 10	71	[68, 74]
13	Week 11	78	[75, 81]
14	Week 12	85	[82, 88]
15	Week 13	92	[89, 95]
16	Week 14	99	[96, 102]
17	Week 15	106	[103, 109]
18	Week 16 (End of Treatment)	113	[110, 127]
19	Week 20	141	[128, 155]
20	Week 24	169	[156, 183]
21	Week 28 (End of Study)	197	>=184

* Study days are calculated from 1st day of dupilumab injection

In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) or end of study (EOS), whichever comes first if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ETV/EOT/EOS are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

For the ePRO data collected daily via IVRS, the analysis visit windows will be implemented following the procedures below:

Step 1: Derive the study day,

- If diary date ≥ 1st injection date, then diary study day=diary date – 1st injection date +1;
- Otherwise diary study day=diary date – 1st injection date

Step 2: Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc, with 7 days interval between visit windows.

7. INTERIM ANALYSIS

No interim analysis is planned.

8. SOFTWARE

All analyses will be done using SAS Version 9.2 or above.

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive/Sensitive Statistical Method	SubgroupAnalysis	Other Analyses
Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16;	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Secondary continuous variables	FAS	MI	MMRM, ANCOVA with LOCF and WOCF	Yes for EASI and NRS endpoints	Line plot
Categorical variables	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test / LOCF	Yes for EASI and NRS endpoints	Histogram

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Events

Screening, Baseline, and Treatment Period

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)	**-35 to -1**	**D1**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)			**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Safety:[7]														
Weight	X	X												
Height	X													
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV Ab, HBsAg, HBcAb, Hep C Ab, TB[11]	X													
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[12]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[13]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

[1] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

[2] For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

[3] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[4] Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[5] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[6] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[7] To be collected before the injection of study drug. ADA samples collected at day 1 (baseline) at Week 16 (EOT), at Week 28 (EOS), and at early termination (ET) will be analyzed for ADA.

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

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

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

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites.

Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6,7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X
Total serum IgE				X	X	X	X	X	X
Antigen-specific IgE samples[11]				X			X	X	X
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[12]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[13]				X			X	X	X

1 The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

2 During an unscheduled visit, any of the study procedures noted may be performed, but not all are required

3 The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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

4 For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

5 Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

6 To be collected before the injection of study drug.

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

8 Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

9 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

10 Select sites only - photograph AD area

[11] Includes: antigen-specific IgE (region-specific allergen panels).
[12] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites
[13] ADA samples collected at day 1 (baseline) at Week 16 (EOT), at Week 28 (EOS), and at early termination (ET) will be analyzed for ADA.

10.3. Criteria for Treatment-Emergent Potentially Clinical Significant Value (PCSV) for Dupilumab AD Studies

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.

Parameter	Treatment Emergent PCSV	Comments
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose Hypoglycaemia Hyperglycaemia	 (≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	 ADA May 2005. ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	

Parameter	Treatment Emergent PCSV	Comments
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria

Parameter	Treatment Emergent PCSV	Comments
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. 5 independent criteria

10.4. SAS Code for EQ-5D Index Utility Scoring

```
/*=================================================================*/;
/*  Aim                       : Derive the EQ5-D index (utility)
*/;
/*  Source for the algorithm : scoring EQ-5D health states (Rosalind Rabin
*/;
/*            (cf. G:\_HE\PRO questionnaire\EQ5D\scoring\YorkTariffx.doc)
*/;
/*  Note                      : UK based population (Dolan, 1997)
*/;
/*  Author                    : Elisheva Smadja
*/;
/*=================================================================*/;

data EUROQOL;   set temp;
   profil= (10000*eqq1cd)+(1000*eqq2cd)+(100*eqq3cd)+(10*eqq4cd)+eqq5cd;
   eq5d=1;
**********Mobility*********;
if eqq1cd=2     then eq5d=eq5d-0.069;
if eqq1cd=3     then eq5d=eq5d-0.314;
********Self-care**********;
if eqq2cd=2     then eq5d=eq5d-0.104;
if eqq2cd=3     then eq5d=eq5d-0.214;
******Usual activities*****;
if eqq3cd=2     then eq5d=eq5d-0.036;
if eqq3cd=3     then eq5d=eq5d-0.094;
*****Pain/discomfort******;
if eqq4cd=2     then eq5d=eq5d-0.123;
if eqq4cd=3     then eq5d=eq5d-0.386;
*****Anxiety/depression*****;
if eqq5cd=2     then eq5d=eq5d-0.071;
if eqq5cd=3     then eq5d=eq5d-0.236;

if (eqq1cd ne 1 or eqq2cd ne 1 or eqq3cd ne 1 or eqq4cd ne 1 or eqq5cd ne 1)
                then eq5d=eq5d-0.081;
if (eqq1cd=3 or eqq2cd=3 or eqq3cd=3 or eqq4cd=3 or eqq5cd=3)
                then eq5d=eq5d-0.269;
if (eqq1cd=. or eqq2cd=. or eqq3cd=. or eqq4cd=. or eqq5cd=.)
                then eq5d=.;
```

run;

10.5. Search Criteria for TEAE of Special Interest/TEAE Syndrome

AESI	Search Criteria
Anaphylactic reactions	Narrow SMQ for "anaphylactic reaction"
Acute allergic reactions that require treatment	• Narrow SMQ for "hypersensitivity" • TEAE occurred due to the medication taken and recoded on ConMed CRF page *Note: Blinded manual adjudication of relevant PTs will be required by the study medical monitor, before database locks*
Severe ISRs that last longer than 24 hours	-HLT = Injection site reactions - Severity = "severe"
Mycosis fungoides or other forms of cutaneous T cell lymphoma	-HLT = "Mycosis fungoides" • Includes LLT = Sezary syndrome • Includes LLT = Cutaneous T-cell lymphoma -PT = "Cutaneous T-cell dyscrasia
Any severe infection	-SOC = Infections and infestations -Severity = "severe
Any infection requiring treatment with parenteral antibiotics	-SOC = Infection and infestations -Action taken for AE = "medication" - ConMed: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = IV, IM
Any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks	-SOC = Infection and infestations -Action taken for AE = "medication" -Check CM: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = PO and Treatment duration >14 days
Any clinical endoparasitosis	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection
Any opportunistic infection[a]	The following HLTs plus PTs: -HLT = Pneumocystis infection -HLT* = Fungal infections NEC -HLT* = Pseudallescheria infections -HLT = Herpes viral infections -HLT = Paracoccidioides infections -HLT = Sporothrix infections -HLT = Cryptosporidia infections -HLT* = Trypanosomal infections -HLT* = Campylobacter infections

AESI	Search Criteria
	-HLT* = Shigella infections -HLT* = Vibrio infections Plus the following PTs -Polyomavirus-associated nephropathy -BK virus infection -Cytomegalovirus infection -Post transplant lymphoproliferative disorder -Progressive multifocal leukoencephalopathy -*Bartonellosis -Blastomycosis -Toxoplasmosis -Coccidioidomycosis -Histoplasmosis -*Aspergillus infection -Systemic candida -Oropharyngeal candidiasis -Cryptococcosis -Listeriosis -Tuberculosis -Nocardiosis -Mycobacterial infection -*Salmonellosis -*Hepatitis B -Herpes zoster -*Strongyloidiasis -Microsporidia infection -Visceral leishmaniasis -*Hepatitis C *Note: *Blinded manual adjudication of relevant PTs under each of HLTs listed above will be required by the study medical monitor, before database locks*
Suicidal behavior	Include the following PTs: -Completed suicide -Suicidal ideation -Suicide attempt -Depression suicidal -Suicidal behavior

[a] The definition of opportunistic infections is referring to the recent consensus guidance for opportunistic infections in the setting of biologic therapy (K L Winthrop 2015).

10.6. Algorithm for RESCUE TREATMENTS

1. **Not required to adjudicate rescue treatment:**
   Post-baseline medications (WHODD-coded) given for indications consistent with AD [1]
   a. Always considered rescue:
      - ATC2 = CORTICOSTEROIDS FOR SYSTEMIC USE
      - ATC2 = IMMUNOSUPPRESSANTS
      - Preferred Drug Name = Ciclosporin
      - Preferred Drug Name = Methotrexate
      - Preferred Drug Name = Mycophenolate sodium
      - Preferred Drug Name = Mycophenolic acid
      - Preferred Drug Name = Mycophenolate mofetil
      - Preferred Drug Name = Azathioprine
      - ATC2 = CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, if used on or after Day 15
      - Preferred Drug Name = Tacrolimus, if used on or after Day 15
      - Preferred Drug Name = Pimecrolimus, if used on or after Day 15
   b. Never considered rescue:
      - ATC2 = EMOLLIENTS AND PROTECTIVES
      - ATC2 = VASOPROTECTIVES
      - ATC2 = ANALGESICS
      - ATC2 = ANTI-ACNE PREPARATIONS
      - ATC2 = TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
      - ATC2 = ANTIBACTERIALS FOR SYSTEMIC USE
      - ATC2 = ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
      - ATC2 = ANTIVIRALS FOR SYSTEMIC USE
      - ATC2 = ANTIFUNGALS FOR DERMATOLOGICAL USE
      - ATC2 = ANTISEPTICS AND DISINFECTANTS
      - ATC2 = ANTIHISTAMINES FOR SYSTEMIC USE
      - ATC2 = ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.
      - ATC2 = ANTIPSORIATICS (except Preferred Drug Name = Methotrexate)
      - ATC2 = GENERAL NUTRIENTS
      - ATC2 = VITAMINS
      - ATC2 = CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, if used before Day 15
      - Preferred Drug Name = Tacrolimus, if used before Day 15
      - Preferred Drug Name = Pimecrolimus, if used before Day 15

2. **Require to adjudicate rescue treatment**

   - All other medications (not noted in 1. above) given for indications consistent with AD[1]
   - Medications noted in 1a above, when given for indications not consistent with AD

[1] Below is a list of indications consistent with AD based on PT level from concomitant medication/procedure data using MedDRA 18.0

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
General disorders and administration site conditions	General signs and symptoms NEC	Xerosis	10048222
Infections and infestations	Bacterial infections NEC	Bacterial infection	10060945
Infections and infestations	Bacterial infections NEC	Eczema impetiginous	10051890
Infections and infestations	Bacterial infections NEC	Skin bacterial infection	10052891
Infections and infestations	Herpes viral infections	Eczema herpeticum	10014197
Infections and infestations	Herpes viral infections	Herpes simplex	10019948
Infections and infestations	Skin structures and soft tissue infections	Dermatitis infected	10012470
Infections and infestations	Skin structures and soft tissue infections	Eczema infected	10014199
Infections and infestations	Skin structures and soft tissue infections	Impetigo	10021531
Infections and infestations	Skin structures and soft tissue infections	Pyoderma	10037632
Infections and infestations	Skin structures and soft tissue infections	Rash pustular	10037888
Infections and infestations	Skin structures and soft tissue infections	Skin infection	10040872
Infections and infestations	Skin structures and soft tissue infections	Subcutaneous abscess	10042343
Infections and infestations	Staphylococcal infections	Staphylococcal infection	10058080
Infections and infestations	Staphylococcal infections	Staphylococcal skin infection	10066409
Infections and infestations	Viral infections NEC	Kaposi's varicelliform eruption	10051891
Injury, poisoning and procedural complications	Skin injuries NEC	Excoriation	10049796

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Dry skin	10013786
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Pain of skin	10033474
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Skin disorder	10040831
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Skin fissures	10040849
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis	10012431
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis atopic	10012438
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Eczema	10014184
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Neurodermatitis	10029263
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Seborrhoeic dermatitis	10039793
Skin and subcutaneous tissue disorders	Erythemas	Erythema	10015150
Skin and subcutaneous tissue disorders	Erythemas	Plantar erythema	10051170
Skin and subcutaneous tissue disorders	Exfoliative conditions	Dermatitis exfoliative	10012455
Skin and subcutaneous tissue disorders	Pruritus NEC	Pruritus	10037087
Skin and subcutaneous tissue disorders	Rashes, eruptions and exanthems NEC	Rash	10037844
Skin and subcutaneous tissue disorders	Urticarias	Urticaria	10046735
Surgical and medical procedures	Analgesia supportive care	Pain management	10056350
Surgical and medical procedures	Hormonal therapeutic procedures NEC	Steroid therapy	10062117
Surgical and medical procedures	Therapeutic procedures NEC	Salvage therapy	10068833

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Protocol: final

- Amendment 2 (05 Feb 2015)
- Amendment 1 (24 Oct 2014)

Statistical analysis plan: original

Statistical analysis plan: final

- Modifications from the Statistical Plan in the Final Protocol
- Modifications from the Previously Approved SAP

Clinical Study Protocol

A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Compound:	Dupilumab
Study Name:	Liberty AD Solo
Clinical Phase:	3
Protocol Number:	R668-AD-1416
Date of Issue:	28 AUG 2014
Scientific/Medical Monitor:	Marius Ardeleanu, MD Senior Director, Clinical Sciences Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis
Site Location(s)	Global
Principal Investigator	Not Applicable
Objective(s)	The primary objective is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe atopic dermatitis (AD). The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD.
Study Design	This is a randomized, double-blind, placebo-controlled, parallel group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28-weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below). After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 to receive once weekly (qw) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, every 2 weeks (q2w) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global

	Assessment (IGA) = 3] vs. severe [IGA = 4] AD) and by region. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic. During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits. The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoints will be determined at week 16. Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not been rescued will be eligible to participate in a maintenance study. Patients who meet these criteria but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20: • patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab • patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 to 4 (whichever comes first). For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28. Safety, laboratory, and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events.
Study Duration	Each patient's participation in the study will be up to approximately 21 weeks or 33 weeks, including the screening period.

Population	
Sample Size:	Approximately 600 patients will be enrolled at approximately 160 global study sites
Target Population:	The study population includes adults 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)
Treatment(s)	
Study Drug Dose/Route/Schedule:	Dupilumab SC Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg dupilumab in a 2 mL volume) on day 1 followed by 300 mg in 2 mL qw from week 1 through week 15 Or Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg in a 2 mL volume) on day 1 followed by 300 mg in 2 mL q2w from week 1 through week 15. The last dose of study drug for both regimens will be at week 15.
Placebo Route/Schedule:	Matching placebo SC injection. Loading dose for the placebo arm consists of 2 injections, each containing placebo formulation in a 2 mL volume, administered at day 1 and followed by qw injections of 2 mL placebo formulation from week 1 through week 15 (last dose of study drug will be at week 15).
Endpoint(s)	During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries.
Primary:	• Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
Co-Primary for European Medicines Agency (EMA) and EMA Reference Market Countries Submissions:	• Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 • Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
Secondary:	• Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA as it is already a co-primary endpoint)

- Percent change from baseline to week 16 in pruritus numerical rating scale (NRS)
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent Body Surface Area (BSA)
- Change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)
- Change from baseline to week 16 in Global Individual Signs Score (GISS) (erythema, infiltration/population, excoriations, lichenification)
- Change from baseline to week 16 in Dermatology Life Quality Index (DLQI)
- Change from baseline to week 16 in Hospital Anxiety Depression Scale (HADS)
- Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of skin infection treatment-emergent adverse events (TEAE) requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

Procedures and Assessments

A variety of parameters will be collected during the study to assess the efficacy of dupilumab, including measures of AD severity, and patient-reported measures of AD symptoms and quality of life (QOL).

The safety of dupilumab in this population will be assessed by evaluating TEAEs, detailed medical history, thorough physical examination, vital signs, electrocardiograms (ECGs), and clinical laboratory testing. Concomitant medications and procedures will be collected from time of informed consent to the end of the study. Safety data will be reviewed on an ongoing basis by the sponsor. An independent data monitoring committee (IDMC) that oversees the entire dupilumab clinical development program will review

	safety data periodically in an unblinded fashion and will advise the sponsor of potential safety signals. Blood samples will be collected for dupilumab concentration and anti-dupilumab antibody (ADA) levels at pre-determined time points. Research samples and samples for exploratory biomarker analysis will be collected.
Statistical Plan	**Sample Size:** To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total with a randomization ratio of 1:1:1 dupilumab, 300 mg qw: 300 mg q2w: placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment) to detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively. The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively. The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. **Efficacy Analysis Set:** The full analysis set (FAS) includes all randomized patients who receive any study medication. Efficacy analysis will be based on treatment allocated at randomization (as randomized), which will be stratified by disease severity and region. **Methods:** For continuous variables, descriptive statistics will include: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category. 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.

Primary Efficacy Analysis

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

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, a mixed-effect model with repeated measures (MMRM) will be used. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary time point, week 16, as well as at the other time points by time point-specific contrasts from the MMRM model.

For the binary efficacy endpoints, if rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used. If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal.

For the continuous efficacy endpoints, if a patient receives rescue medication, the data collected after rescue medication is initiated will be treated as missing.

Sensitivity analysis using other missing data handling approaches will also be performed.

Multiplicity Considerations

For US and US reference market submissions: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For the comparison of each dose regimen with placebo, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section of secondary endpoints.

For EMA and EMA reference market submissions: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the

co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section on section endpoints.

Safety Analysis: Will be based on the SAF. This includes TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and ECG results). A summary of safety results for each treatment group will be presented.

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Appendix 1: Factors to Consider in Assessing the Relationship of AEs to Study Drug

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibody
Anti-dsDNA	Anti-nuclear antibody against double-stranded DNA
Anti-TPO	Anti-thyroid peroxidase antibody
ARGUS	A Pharmacovigilance and Risk Management Safety Software System
AST	Aspartate Aminotransferase
BSA	Body surface area of involvement of atopic dermatitis
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full analysis set
GCP	Good Clinical Practice
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFNγ	Interferon gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin

IL-4Rα	Interleukin-4 receptor alpha
IRB	Institutional Review Board
ISR	Injection site reactions
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
NRS	Numerical rating scale
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PT	Preferred term
QOL	Quality of life
qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
TARC	Thymus and activation-regulated chemokine (CCL-17)
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (ie, itchiness), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD (Bieber 2008).

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction.

Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, hypothalamic pituitary axis effects, Cushing's disease, etc.). Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants (Schmitt 2007) and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation.

Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids (Schmitt 2009, Schram 2012, Akhavan 2008). Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

Up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents (Hart 2002, Wenzel 2007).

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. This population includes patients who are often treated with systemic corticosteroids, as well as other non-selective immunosuppressants, including cyclosporine, which are associated with significant toxicities. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. As of the cut-off date (28 March, 2014), there has been no evidence in the ongoing phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab for up to 12 weeks.

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 is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients 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). This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab.

1.2.2. Rationale for Dose Selection

The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). All patients randomized to receive treatment with dupilumab will get an initial loading dose of 600 mg on day 1. 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.

The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021), which evaluated dupilumab dose regimens of 300 mg qw, 300 mg q2w, 300 mg every 4 weeks (q4w), 200 mg q2w, and 100 mg q4w, versus placebo, administered for 16 weeks. An interim analysis was conducted after 240 patients completed 12 weeks of treatment. The interim analysis, which focused primarily on week 12 outcomes, indicated that dupilumab 100 mg q4w had suboptimal efficacy, whereas the 300 mg qw dupilumab regimen demonstrated the highest efficacy and was comparable to other dupilumab dosing regimens with respect to safety parameters. Therefore, the 300 mg qw dose was selected for further evaluation in phase 3 together with a 300 mg dose administered less frequently, q2w. Both doses were selected to be evaluated in this study to further refine the understanding of dose-response relationships in a larger sample of study patients and to explore a dose regimen with less frequent administration.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients 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 confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below).

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 at least 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 to receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by region (details will be specified in the interactive voice response system/interactive web response system [IVRS/IWRS] specifications document). Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks (Figure 1). Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Table 1 and Table 2).

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in a maintenance study. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

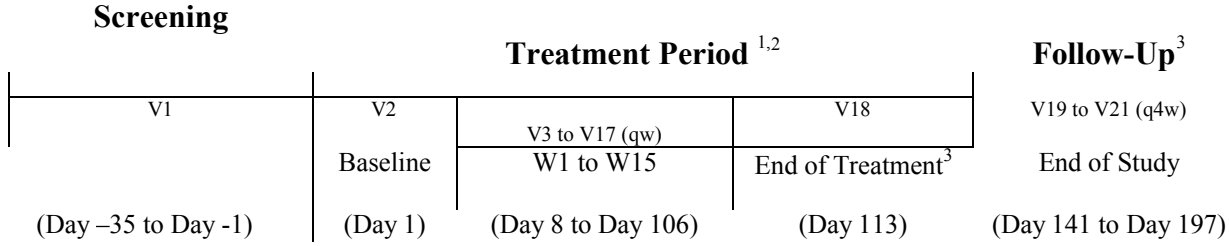
- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of

quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Patients with an ADA titer of ≥240 at their last study visit and some patients who are negative for ADA at their last study visit will be asked to return to the clinic to have additional ADA samples collected for analysis (see section 6.3.4.2 for details and time points).

Figure 1: Study Flow Diagram



[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered.

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

3.2. Planned Interim Analysis

No interim analysis is planned.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An independent data monitoring committee (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 is 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 600 patients will be enrolled at approximately 160 global sites.

4.2. Study Population

The study population consists of adults 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).

4.2.1. Inclusion Criteria

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

1. Male or female, 18 years or older
2. Chronic AD, (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]), that has been present for at least 3 years before the screening visit
3. EASI score ≥16 at the screening and baseline visits
4. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits
5. ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits
6. Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks

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 (±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 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 re-screened after such documentation is obtained (ie, patients are shown to fail a 28-day course of mid-to-higher potency TCS [±TCI]).

7. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least 7 days before the baseline visit (NOTE: See exclusion criterion #6 for limitations regarding emollients)
8. Willing and able to comply with all clinic visits and study-related procedures
9. Able to understand and complete study-related questionnaires
10. Provide signed informed consent

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 an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
3. 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:
   - Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
   - Phototherapy for AD
4. Treatment with TCS or TCI within 1 week before the baseline visit
5. Treatment with biologics as follows:
   - Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte count returns to normal, whichever is longer
   - Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer
6. 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)
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit
8. Planned or anticipated use of any prohibited medications (see section 5.7.1) and procedures during study treatment
9. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit

10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: patients may be rescreened after infection resolves.
11. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per investigator judgment
12. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
13. Positive with hepatitis B surface antigen (HBsAg) or hepatitis C antibody at the screening visit
14. At baseline, presence of any conditions listed as criteria for study drug discontinuation (see section 5.4.2)
15. Presence of skin comorbidities that may interfere with study assessments
16. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
17. 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
18. History of alcohol or drug abuse within 2 years of the screening visit
19. 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 (HbA1c $\geq$ 9%), patients with cardiovascular conditions (eg, stage 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 [CRFs], etc.).
20. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may 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, CRFs, etc.)

21. Planned or anticipated major surgical procedure during the patient's participation in this study
22. Patient is a member of the investigational team or his/her immediate family
23. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
24. Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 120 days after last dose of study drug. These include hormonal contraceptives, intrauterine device, or double barrier contraception (ie, condom + diaphragm) or a 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

    *For females, menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone level of ≥25 mU/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception

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 investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, adverse event (AE), treatment failure, protocol violation, cure, and for administrative, or other reasons. An excessive rate of withdrawals would diminish the informative value of the study data; therefore, unnecessary withdrawal of patients should be avoided. Patients who discontinue study treatment but who consent to remain in the study will continue to comply with study visits and assessments.

Patients who withdraw prematurely from the study will be asked to complete study assessments per section 6.2.5.

See section 3.1 for details of the maintenance and OLE studies.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

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

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

Patients will receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or weekly injections of matching placebo (following a placebo "loading dose") during the 16-week treatment period.

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 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 3 and 4 (weeks 1 and 2, respectively) and all other visits in the clinic. 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], 3 [day 8], and 4 [day 15]) and blood pressure and heart rate determined. The patient (or caregiver) will administer study drug outside of the clinic during weeks in which no clinic visit is scheduled.

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

The procedure for preparing the dupilumab dose for SC injection will be provided in the pharmacy manual. Subcutaneous injection sites 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 (ISRs), study drug should be administered only into areas of normal-looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual.

Detailed instructions for transport, storage, preparation, and administration of study drug will be provided by the site to the patient (or caregiver). Patients will complete a dosing diary to document compliance with self-injection of study drug outside the clinic.

5.2. Background Treatment

All patients are required to apply moisturizers at least twice daily for at least 7 days before randomization and to continue the treatment throughout the study (all 28 weeks where applicable). 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(s)

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. For the purpose of efficacy

analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication. All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

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 temporarily or 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 and complete all study assessments per the study schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per section 6.2.5.

5.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Evidence of pregnancy.
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status.
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks.
- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5 \times 10^3$ µL.

- Platelet count ≤50 x 10^3 µL.
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3x upper limit of normal (ULN) with total bilirubin >2x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome).
- Confirmed AST and/or ALT >5x 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).

- Other reasons that may lead to the permanent discontinuation of study treatment include:
  - Treatment with any prohibited concomitant medication or procedure (section 5.7.1).

5.4.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count ≤1.0 x 10^3/µL but >0.5 x 10^3/µL.
  - Platelet count ≤100 x 10^3/µL but >50 x 10^3/µL.
  - Creatine phosphokinase (CPK) >10x ULN.
- Other intercurrent illnesses or major surgery.

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 600 patients will be randomized on day 1 in a 1:1:1 ratio to receive qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo for 16 weeks. Patients will be randomized to a treatment group according to a central randomization scheme provided by an IVRS/IWRS to the designated site personnel or clinical staff members. Randomization will be stratified by disease severity (IGA 3 vs IGA 4) and

region (details will be specified in the IVRS/IWRS specifications document and will be documented in the clinical study report).

5.5.1. Blinding

With the exception of the statistician who provides the randomization sequence, the IDMC statistician, the IDMC members, and the provisions in section 5.5.2, this study will remain blinded to all individuals until the pre-specified 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 weekly injections of dupilumab or placebo starting at day 1. During weeks in which dupilumab is not administered in the q2w dosing regimen, patients will receive placebo.

Anti-drug antibody and drug concentration results will not be communicated to the sites, and the sponsor 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 the treatment assignment for a patient may be necessary due to a medical emergency, a serious adverse event (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). Details for emergency unblinding will be provided in the study manual.

- 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 at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2°C to 8°C 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

Any treatment administered from the time of informed consent 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 through week 16:

- Treatment with a live (attenuated) vaccine.
- Treatment with an investigational drug (other than dupilumab).
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine.
- Treatment with an investigational drug (other than dupilumab).
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

NOTE: If a patient receives treatment with systemic corticosteroids or other systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

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.

5.7.2.1. Cytochrome P450

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized.

However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (Abdel-Razzak 1993, Christensen 2012). Human peripheral blood mononuclear cells incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (Liptrott 2009).

Limited in vitro findings suggest that IL-4 and IL-13 may affect CYP levels and potentially activities. However, the clinical significance of these data is not fully understood. During the study treatment and at least up to the end of follow-up, investigators are cautioned to monitor clinical and laboratory signs that might indicate a potential drug-drug interaction in all patients receiving dupilumab concomitantly with narrow therapeutic index medications that are metabolized by CYP (see Investigator's Brochure for more details of such drugs). This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal, if needed.

For more details, refer to the study manual.

5.7.2.2. Prohibited Concomitant Medications or Procedures as Rescue

If medically necessary (eg, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator (see section 5.3 for details).

Blinded adjudication of concomitant medications may be performed to identify concomitant medications that confound study endpoints.

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 and Table 2.

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

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												
Safety:[7]														
Weight	X	X												
Height	X													
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV ab, HBsAg, Hep C Ab, TB[11]	X													
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[12]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[13]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

1 The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

2 For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

3 Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

4 Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

5 For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

6 Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

7 To be collected before the injection of study drug.

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

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

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

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs. A sub-study conducted at selected sites.

Table 2: Schedule of Events – (Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination)

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6,7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Total serum IgE				X	X	X	X	X	X
Antigen-specific IgE samples[11]				X			X	X	X
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[12]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[13]				X			X	X	X

[1] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

[2] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required

[3] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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

[4] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[5] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[6] To be collected before the injection of study drug.

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

[8] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

[11] Includes: antigen-specific IgE (region-specific allergen panels).

[12] Non-invasive skin swabs. A sub-study conducted at selected sites

[13] Patients with an ADA titer of ≥240 at the last study visit will be asked to return to the clinic to have additional samples collected for analysis (see section 6.3.4.2 for details and time points).

6.2. Study Visit Descriptions

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

1. Patient Reported Outcomes.
2. Investigator assessments (performed only by adequately trained investigators or sub-investigators; the same investigator or sub-investigator should perform all the evaluations for a given patient throughout the entire study period).
3. Safety and laboratory assessments.
4. Administration of study drug

6.2.1. Visit 1/Screening/Day –35 to Day -1

After the patient has provided informed consent, the following information will be collected:

- Informed consent for optional assessments (for patients who consent to participate in the genomic sub-study)
- Inclusion/exclusion
- Medical history and concurrent illnesses
- Demographics
- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Training on IVRS
- Pruritus Numerical Rating Scale (NRS)
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - Patient Oriented Eczema Measure (POEM)
  - Hospital Anxiety and Depression Scale (HADS)
  - Dermatology Life Quality Index (DLQI)
  - European Quality of Life-5 Dimensions (EQ-5D)
  - Asthma Control Questionnaire (ACQ-5)
  - Sinonasal Outcome Test (SNOT-22)
- Patient Global Assessment of Disease
- Vital signs
- Investigator's Global Assessment (IGA)

- Eczema Area and Severity Index (EASI)
- Global Individual Signs Score (GISS)
- SCORing Atopic Dermatitis (SCORAD)
- Body Surface Area of (BSA) involvement of atopic dermatitis
- Weight
- Height
- Physical examination
- Electrocardiogram (ECG)
- Laboratory testing:
  - HIV ab
  - HBsAg
  - Hepatitis C antibody
  - TB testing (on a country-by-country basis)
  - Hematology and Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - Thymus activation-regulated chemokine (TARC)
  - Total serum IgE
  - Antigen-specific IgE (region-specific allergen panels)
  - Highly sensitive C-reactive protein (hs-CRP)
  - Anti-nuclear antibody (ANA)
  - Anti-double-stranded DNA (anti-dsDNA)
  - Anti-thyroid peroxidase (anti-TPO)
  - Skin microbiome samples (select sites)
  - Research samples

6.2.2. Treatment Period

6.2.2.1. Visit 2/Baseline/Day 1

The following information will be collected:

- Inclusion/Exclusion
- Concomitant medications

- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology and Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA

  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - DNA and RNA samples
  - Functional dupilumab pharmacokinetic (PK) sample
  - Anti-dupilumab antibody sample
- Randomization
- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.2. Visit 3/Week 1/Day 8 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA

- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.3. Visit 4/Week2/Day 15 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample

- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection
- Provide patient dosing diary
- Study drug dispensation

6.2.2.4. Visit 5/Week 3/Day 22 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.5. Visit 6/Week 4/Day 29 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment

- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.6. Visit 7/Week 5/Day 36 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.7. Visit 8/ Week 6/Day 43 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.8. Visit 9/Week 7/Day 50 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS

- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.9. Visit 10/ Week 8/Day 57 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE

  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.10. Visit 11/Week 9/Day 64 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.11. Visit 12/Week 10/Day 71 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.12. Visit 13/Week 11/Day 78 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.13. Visit 14/Week 12/Day 85 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD

- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.14. Visit 15/Week 13/Day 92 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.15. Visit 16/Week 14/Day 99 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administer study drug.
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.16. Visit 17/Week 15/Day 106 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.17. Visit 18/End of Treatment/Week 16/Day 113 (±3 days)

The end of treatment at week 16 (visit 18) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment

- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.3. Follow-up Period

6.2.3.1. Visit 19/Week 20/Day 141 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.3.2. Visit 20/Week 24/Day 169 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.4. Visit 21/End of Study Visit/Week 28/Day 197 (±3 days)

The end of study at week 28 (visit 21) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:

  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient global assessment of disease
- Patient global assessment of treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)

- Research samples
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

6.2.5. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 16) will be asked to return to the clinic for 2 visits: once for early termination assessments, and again at week 16 (primary endpoint visit), as described in section 6.2.2.17. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA

- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.6. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. During an unscheduled visit, any of the procedures noted may be performed, but not all are required.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)

- Research samples
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

Assessments performed only at the screening and/or baseline visit include: medical history, medication history, demographics, diagnosis of chronic AD, HBsAg, anti-HIV antibody, and hepatitis C antibody. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

6.3.2. 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 will be administered only to the subset of patients who fluently speak a language in which the assessment tool has been translated. These 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 POEM, HADS, DLQI, and EQ-5D).

6.3.2.1. Patient Assessment of Pruritus

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average 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 overall (on average) during the previous 24 hours?"
- 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.2. Patient-Assessed Pruritus Categorical Scale

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in 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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.3. 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 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 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 6.2.

The POEM is provided in the study reference manual.

6.3.2.4. 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 6.2.

The HADS is provided in the study reference manual.

6.3.2.5. Patient-Reported Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL (Badia 1999). The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. 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 6.2.

The DLQI is provided in the study reference manual.

6.3.2.6. Patient-Assessed EQ-5D

The EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement (ie, no problems, some problems, or severe problems) in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

The EQVAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)". This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

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 6.2.

The EQ-5D is provided in the study reference manual.

6.3.2.7. Patient Global Assessment of Disease

Patients will rate their overall wellbeing based on a 5-point Likert scale from poor to excellent. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent." Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.8. Patient Global Assessment of Treatment

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent". Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.9. Juniper Asthma Control Questionnaire

The 5-question version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.10. Sinonasal Outcome Test

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.11. Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.12. 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 6.2.

The IGA is provided in the study reference manual.

6.3.2.13. 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 6.2.

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

6.3.2.14. Body Surface Area Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 6.2.

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

6.3.2.15. 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. The GISS will be assessed at time points according to section 6.2.

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

6.3.2.16. SCORing Atopic Dermatitis

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). There are 3 components to the assessment: A = extent or affected body surface area, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see section 6.3.2.14) 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, 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 VAS, 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 6.2.

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

6.3.2.17. 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 (pre-dose). Subsequent photographs of the same area will be taken at week 16 (end of treatment) and week 28 (end of study).

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

6.3.3. Safety Procedures

6.3.3.1. Physical Examination

A thorough and complete physical examination will be performed at time points according to section 6.2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

6.3.3.2. Weight and Height

Weight and height will be determined at time points according to section 6.2.

6.3.3.3. Vital Signs

Vital signs, including heart rate, blood pressure, body temperature, and respiration rate, will be collected pre-dose at time points according to section 6.2. Vital signs (blood pressure and heart rate) will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation.

6.3.3.4. Electrocardiogram

Electrocardiograms will be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to section 6.2. The ECG strips or reports will be retained with the source documentation, and the results will be documented in the electronic case report form.

Electrocardiogram results will be interpreted by a central reading center. Instructions for performing the assessment and transmitting ECG data are provided in the study reference manual.

6.3.3.5. Laboratory Testing

Hematology, chemistry, urinalysis, and serum pregnancy testing samples will be analyzed by a central laboratory. The urine pregnancy test kit will be provided to the site by the laboratory.

Blood samples for serum chemistry and hematology testing will be collected to measure overall patient health at screening. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. 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 6.2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK

Hematology

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

Urinalysis

Microscopic analysis will only be done in the event of abnormal dipstick results.

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

Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at time points according to section 6.2.

Testing for HIV antibody, HBsAg, and hepatitis C antibody will be performed at screening. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or

conditions unrelated to the study medication or its administration, the medical monitor must be consulted.

- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in section 7.2.5.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Samples for dupilumab concentration will be collected at time points listed in section 6.2.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in section 6.2.

Patients with an ADA titer of ≥240 at their last study visit (early termination or end of study) will be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months, until their titers fall below 240. Some patients who are negative for ADA at their last study visit will also be asked to return to the clinic within 6 to 12 months from their last dose of study drug to have additional ADA samples collected to maintain the blind.

6.3.5. Research Testing

Research assessments are performed for exploratory purposes only; results for assessments in the sub-sections below will not be reported in the clinical study report. Results will be reported separately from the clinical study report.

6.3.5.1. Research Samples

Research samples (serum/plasma) will be collected at time points according to section 6.2.

Use and Storage of Research Samples (Serum/Plasma)

Research serum and plasma samples will be collected to study the effects of the study drug on modulation of the IL-4 receptor as well as on atopic disease processes. Unused samples collected for drug concentration or ADA analyses may also be used for other research purposes. Remaining samples may be stored (up to 10 years) for future use in experiments related to AD or related diseases. If necessary, the samples may also be used to identify markers associated with toxicity.

6.3.5.2. Genomics Sub-Study - Optional

Patients will be asked to participate in an optional genomics sub-study. Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study informed consent form (ICF) before collection of the samples. Blood for DNA extraction should

be collected on day 1/baseline (pre-dose), but may be collected at any study visit. RNA samples will be collected at time points according to section 6.2. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA and RNA samples for the genomics sub-study will be double-coded as defined by the ICH guideline E15. Sub-study samples may be stored for up to 10 years after the final date of the clinical study report and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to IL-4/13 pathway inhibition (via IL-4Rα blockade), atopic disease risk, prognosis and progression, or other clinical outcome measures. These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Genome-wide studies, including (but not limited to) single nucleotide polymorphism analyses and genomic sequencing may also be performed. If indicated, genomic analyses may also be performed to identify markers associated with toxicity.

6.3.5.3. Exploratory Biomarker Testing

Biomarkers to be analyzed in this study are: TARC, total serum IgE, antigen-specific IgE (region-specific, allergen-specific panels), *S. aureus* enterotoxin A-specific IgE, *S. aureus* enterotoxin B-specific IgE, hs-CRP, ANA, anti dsDNA, anti-TPO. Skin swab samples for skin microbiome testing will be banked. Samples will be collected at time points according to section 6.2. These are exploratory assessments to further the understanding of AD-associated biomarkers and the response to dupilumab treatment. The results of these tests will not be used to evaluate patient eligibility for study participation.

Thymus and activation regulated chemokine and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug. These results may also 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, and will be evaluated as an exploratory marker of efficacy. These markers may also be assessed for their potential value in predicting treatment response.

Staphylococcus aureus colonization and infection on the skin is a significant complication for many AD patients. To determine whether or not dupilumab treatment can reduce colonization and/or infection, exploratory samples for skin microbiome analyses will be banked. Non-invasive skin swab samples from lesional and non-lesional skin will be collected to characterize the skin microbiome diversity and *S. aureus* abundance. Skin swab samples for culturing (eg, semi-quantitative analysis of methicillin-sensitive and methicillin-resistant *S. aureus* colonization) may also be collected.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs 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 also be tested for predictive utility.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti dsDNA, anti-TPO, and ANA) will be measured.

Detailed instructions for sample collection are provided in the laboratory manual.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

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

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

7.1.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as 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).

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 16 weeks 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 in this study include:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Severe ISRs that last longer than 24 hours
- Mycosis fungoides or other forms of cutaneous T cell lymphoma
- Any severe infection; any infection requiring treatment with parenteral antibiotics/anti-viral/anti-fungal agent; any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks; any clinical endoparasitosis; any opportunistic infection

Note: Generally, all uncommon, atypical, peculiar, or unusually persistent infections, especially viral infections, should be reported as AESIs.

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.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

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

Is there a reasonable possibility that the adverse event was 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

A list of factors to consider in assessing the relationship of AES to study, see Appendix 1.

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, AD history and characteristics, and medication history.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoint

During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries. As a result:

The primary endpoint is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Medicines Agency (EMA) and EMA Reference Market Countries only, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

8.2.2. Secondary Endpoints

The secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in HADS
- Change from baseline to week 16 in POEM
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of skin infection treatment-emergent adverse events (TEAE) requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

8.2.3. Other Endpoints and Assessments

- Absolute and percent change from baseline to week 16 in: EQ-5D, Patient Global Assessment of Disease and Patient Global Assessment of Treatment
- Distribution of disease severity scores (eg, IGA, EASI, SCORAD) and their change from baseline
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Changes in efficacy parameters through week 16
- Characterization of dupilumab serum concentrations through week 16

- Correlation analyses:
  - Body weight vs serum concentrations
  - Serum concentrations vs clinical outcomes
  - Body weight vs clinical outcomes
  - Association between baseline biomarkers (eg, TARC, total IgE) and clinical response
- Incidence of dupilumab ADA

8.3. Pharmacokinetic Variables

The PK variables may include, but are not limited to, the following:

- C_{trough} over time
- C_{last}
- T_{last}
- Time to steady state
- $C_{troughSS}$ - steady state trough concentration

8.4. Anti-drug Antibody Variables

ADA variables include status (positive or negative) and titer as follows:

- Total positive at any time
- Pre-existing immunoreactivity - a positive ADA response at baseline
- Treatment emergent - defined as either any positive response when baseline results are negative, or if any post treatment ADA response is ≥4-fold over baseline titer levels
- Persistently positive
- Transiently positive
- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

If a sample tests positive for ADA, the neutralizing activity of the ADA will be assessed.

9. STATISTICAL PLAN

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

Analysis variables are listed in section 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

Disease severity and region 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

To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo.

9.3. Analysis Sets

9.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients who receive any study medication. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

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). If a patient receives a dose regimen different to that assigned during the study, this patient will be considered as treated by the lowest active dose

regimen. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

9.3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all randomized patients with at least 1 post-baseline drug concentration result.

9.3.4. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all randomized patients with at least 1 post-baseline ADA result.

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, median, standard deviation, 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. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

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 (region, disease severity) will be used for the percentage of patients with IGA 0 or 1 at week 16 or percentage of patients with EASI-75 at week 16.

To account for the impact of rescue medication on the efficacy effect:

For the binary efficacy endpoints, if rescue medication is used (see section 5.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.

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

Sensitivity analysis using 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.

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, a mixed-effect model with repeated measures (MMRM) will be used, which will account for the missing data. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. The MMRM model will provide baseline adjusted least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p-values for treatment comparisons by the appropriate time point-specific contrasts from the model. Additional details on the MMRM model will be provided in the SAP.

To account for the impact of rescue medication on the efficacy effect:

Continuous efficacy endpoints: if a patient receives rescue medication that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue medication is initiated will be treated as missing.

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

In addition to the MMRM model, sensitivity analysis using LOCF and/or the multiple imputation (MI) methods followed by an analysis of covariance model will be conducted. Robustness of the MMRM model to departure from the missing-at-random assumption will be explored using sensitivity analysis based on the pattern mixture model plus MI approach. Additional details on these sensitivity analyses will be provided in the SAP.

9.5.2.3. Multiplicity Considerations

For US and US Reference Market Countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the

2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

For EMA and EMA reference market submissions:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients achieving EASI-75 (≥75% reduction from baseline in EASI score at week 16 (this is not a secondary endpoint for the EMA as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in HADS
- Change from baseline to week 16 in POEM
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16
- Incidence of TESAEs from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

9.5.3. Safety Analysis

Safety analysis will be based on the SAF. This includes reported TEAEs and other safety information (ie, 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 pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug (day 1) to the end of the study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing 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 patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

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

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

9.5.3.2. Other Safety

Vital Signs

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

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.

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

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for 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 and calculated as:

(Date of last study drug injection – date of first study drug injection) + 7 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:

Treatment Compliance =

(Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) x 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

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

9.5.5. Analysis of Anti-Drug Antibody Data

The ADA variables described in section 8.4 will be analyzed using descriptive statistics. Drug concentration data will be examined and the influence of ADAs on individual concentration-time

profiles will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

9.5.6. Analysis of Quality of Life Data

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

9.5.7. 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-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 non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

The CRF data for this study will be collected with an electronic data capture 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, study drug supply
- EDC system – data capture/uploading and storing photographs
- Statistical Analysis Software (SAS) – statistical review and analysis
- ARGUS – a PVRM Safety System
- nQuery Advisor – sample size calculations

11. STUDY MONITORING

11.1. Monitoring of Study Sites

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

11.2. Source Document Requirements

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

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

11.3. Case Report Form Requirements

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

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

12. AUDITS AND INSPECTIONS

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

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

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

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

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) must be kept in strict confidence.

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

13.4. Institutional Review Board/Ethics Committee

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

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study

- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

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

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

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments),

breach of the applicable laws and regulations, or breach of any applicable ICH guidelines

- The total number of patients required for the study are enrolled earlier than expected

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

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

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS dated 28 AUG 2014, and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

Appendix 1: Factors to Consider in Assessing the Relationship of AEs to Study Drug

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

No:

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

Yes:

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

NOTE: This list is not exhaustive.

Clinical Study Protocol

A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Compound:	Dupilumab
Study Name:	Liberty AD SOLO 2
Clinical Phase:	3
Protocol Number:	R668-AD-1416
Protocol Version:	R668-AD-1416.02
Amendment 2 Date of Issue:	05 FEB 2015
Amendment 1 Date of Issue:	24 OCT 2014
Original Date of Issue:	28 AUG 2014
Scientific/Medical Monitor:	Marius Ardeleanu, MD Senior Director, Clinical Sciences Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

Confidential: This document contains confidential information that is the property of Regeneron Pharmaceuticals, Inc., and must not be disclosed to anyone other than designees of Regeneron for the conduct of the study, the recipient clinical Investigator(s) and their designees and members of the Institutional Review Board. This information must not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Regeneron Pharmaceuticals, Inc.

AMENDMENT 2 (05 FEB 2015)

The purposes of amendment 2 are to:

- Add text to indicate that for background treatment with moisturizers (emollients), to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit
- Change the terminology of "European Medicines Agency (EMA) reference market" to "European Union (EU) reference market"
- Separate the secondary endpoints into 2 parts: Key Secondary Endpoints and Other Secondary Endpoints
- Rearrange "other secondary endpoints": move up "change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)" to be above the endpoint "change from baseline to week 16 in Hospital Anxiety Depression Scale (HADS)"
- Revise the following endpoints in the "other secondary endpoints" section: from "change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)" to "percent change from baseline to week 16 in SCORAD"; from "change from baseline to week 16 in Global Individual Signs Score (GISS) (erythema, infiltration/population, excoriations, lichenification)" to "percent change from baseline to week 16 in GISS (erythema, infiltration/population, excoriations, lichenification)"
- Move the following secondary endpoint to the end of "other secondary endpoints": "incidence of skin infection treatment-emergent adverse events (TEAEs) requiring systemic treatment from baseline through week 16"
- Revise the definition for the full analysis set (FAS) from "the FAS includes all randomized patients who receive any study medication" to "the FAS includes all randomized patients", and add per protocol set (PPS) for efficacy analysis
- Add description of methods for missing data imputation (multiple imputation [MI] Statistical Analysis Software [SAS] procedure with Markov Monte Carlo algorithm) and data analysis (analysis of covariance [ANCOVA] and the SAS MIANALYZE procedure) for continuous secondary endpoints to be used in US and US reference market countries, and revise text relevant to this topic
- Add an inclusion criterion requiring a patient to have a baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥3 to be eligible to enroll in the study
- Revise footnote 13 of Table 1 and footnote 12 of Table 2 to clarify that non-invasive skin swabs is a sub-study that may be (instead of "will be", as previously stated) conducted at selected sites

- Clarify that instructions for performing the assessment and transmitting electrocardiogram (ECG) data are provided in the central ECG reference manual, instead of the study reference manual (as previously stated)
- Add the following as a potential use of research samples: to study biomarkers that may have predictive utility for response to dupilumab treatment
- For exploratory biomarker testing, change the phrase from "… samples … will be banked" to "… samples … may be banked"
- Revise the language for the endpoint "changes in efficacy parameters through week 16" in the "other endpoints and assessments" section to include absolute and percent changes in efficacy parameters through week 16
- Add description for a sensitivity analysis for binary endpoints
- Make editorial changes for clarity and/or consistency

The following table outlines the changes made to protocol R668-AD-1416.02 and the affected sections:

Change	Section Changed
Add text to indicate that for background treatment with moisturizers (emollients), to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit	Synopsis: Study Design Section 3.1 Study Description and Duration Section 4.2.1 Inclusion Criteria - Inclusion Criterion #8 Section 5.2 Background Treatment
Change the terminology of "EMA reference market" to EU reference market"	Synopsis: Endpoints (Co-primary and Secondary); Statistical Plan Section 8.2.1 Primary Endpoint Section 8.2.2 Secondary Endpoints Section 9.5.2.2 Secondary Efficacy Analysis Section 9.5.2.3 Multiplicity Considerations
Separate the secondary endpoints into 2 parts: Key Secondary Endpoints and Other Secondary Endpoints	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints
Rearrange "other secondary endpoints": move up "change from baseline to week 16 in POEM" to be above the endpoint "change from baseline to week 16 in HADS"	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints Section 9.5.2.3 Multiplicity Considerations
Revise the following endpoints in the "other secondary endpoints" section: from "change from baseline to week 16 in SCORAD" to "percent change from baseline to week 16 in SCORAD"; from "change from baseline to week 16 in GISS (erythema, infiltration/population, excoriations, lichenification)" to "percent change from baseline to	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints Section 9.5.2.3 Multiplicity Considerations

week 16 in GISS (erythema, infiltration/population, excoriations, lichenification)"	
Move the following endpoint to the end of "other secondary endpoints": "incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16"	Synopsis: Endpoints (Secondary) Section 8.2.2 Secondary Endpoints Section 9.5.2.3 Multiplicity Considerations
Revise the definition for the FAS from "the FAS includes all randomized patients who receive any study medication" to "the FAS includes all randomized patients," and add PPS for efficacy analysis	Synopsis: Statistical Plan Section 9.3.1 Efficacy Analysis Sets
Add description of methods for missing data imputation (MI SAS procedure with Markov Monte Carlo algorithm) and data analysis (ANCOVA and the SAS MIANALYZE procedure) for continuous secondary endpoints to be used in US and US reference market countries, and revise text relevant to this topic	Synopsis: Statistical Plan Section 9.5.2.2 Secondary Efficacy Analysis
Add an inclusion criterion requiring a patient to have a baseline Pruritus NRS average score for maximum itch intensity ≥3 to be eligible to enroll in the study	Section 4.2.1 Inclusion Criteria - Inclusion Criterion #6 (added)
Revise footnote 13 of Table 1 and footnote 12 of Table 2 to clarify that non-invasive skin swabs is a sub-study that may be (instead of "will be", as previously stated) conducted at selected sites	Table 1 Schedule of Events (Screening, Baseline, and Treatment Period) - footnote 13 Table 2 Schedule of Events – (Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination) - footnote 12 Section 6.3.5.3 Exploratory Biomarker Testing
Clarify that instructions for performing the assessment and transmitting ECG data are provided in the central ECG reference manual, instead of the study reference manual (as previously stated)	Section 6.3.3.4 Electrocardiogram
Add the following as a potential use of research samples: to study biomarkers that may have predictive utility for response to dupilumab treatment	Section 6.3.5.1 Research Samples
For exploratory biomarker testing, change the phrase from "… samples … will be banked" to "… samples … may be banked"	Section 6.3.5.3 Exploratory Biomarker Testing
Revise language for the endpoint "changes in efficacy parameters through week 16" in the "other endpoints and assessments" section to include "absolute and percent changes in efficacy parameters through week 16"	Section 8.2.3 Other Endpoints and Assessments

Add description for a sensitivity analysis for binary endpoints	Section 9.5.2.1 Primary Efficacy Analysis
Editorial changes for clarity and/or consistency	Amendment 1 Summary Synopsis: Statistical Plan List of Abbreviations and Definitions of Terms Section 5.2 Background Treatment Section 5.4.2.1 Reasons for Permanent Discontinuation of Study Drug Table 1 Schedule of Events (Screening, Baseline, and Treatment Period), row for HIV Ab Section 6.2.1 Visit 1/Screening/Day –35 to Day -1 Section 8.2.2 Secondary Endpoints Section 9.5.2.2 Secondary Efficacy Analysis

AMENDMENT 1 (24 OCT 2014)

The purposes of amendment 1 are to:

- Update emollient use
- Clarify exclusion criterion #7
- Add positive hepatitis B core antibody (HBcAb) as an exclusion
- Clarify rescue treatment
- Modify section on discontinuation of study drug
- Change the time period for prohibition of listed medications from “through week 16” to “during the study”
- Add immunomodulating biologics to the list of prohibited medications
- Modify frequency of patient self-assessment for pruritus
- Specify that fasting is recommended prior to collecting blood samples for laboratory testing
- Add provision for additional tests when total bilirubin is > upper limit of normal (ULN) and creatine phosphokinase (CPK) is >5X ULN
- Make minor edits

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis
Site Location(s)	Global
Principal Investigator	Not Applicable
Objective(s)	The primary objective is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe atopic dermatitis (AD). The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD.
Study Design	This is a randomized, double-blind, placebo-controlled, parallel group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28-weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below). After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 (emollients) twice daily for at least the 7 consecutive days immediately 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 non-lesional skin designated for such assessments for at least 8 hours before each clinic visit. Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio to receive once weekly (qw) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, every 2 weeks (q2w) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) = 3] vs. severe [IGA = 4] AD) and by region. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits. The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoints will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not been rescued will be eligible to participate in a maintenance study. Patients who meet these criteria but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 to 4 (whichever comes first).

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Safety, laboratory, and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events.

Study Duration	Each patient's participation in the study will be up to approximately 21 weeks or 33 weeks, including the screening period.
Population	
Sample Size:	Approximately 600 patients will be enrolled at approximately 160 global study sites
Target Population:	The study population includes adults 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)
Treatment(s)	
Study Drug	Dupilumab SC
Dose/Route/Schedule:	Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg dupilumab in a 2 mL volume) on day 1 followed by 300 mg in 2 mL qw from week 1 through week 15 Or Patients will receive a loading dose of 600 mg (2 injections each containing 300 mg in a 2 mL volume) on day 1 followed by 300 mg in 2 mL q2w from week 1 through week 15. The last dose of study drug for both regimens will be at week 15.
Placebo Route/Schedule:	Matching placebo SC injection. Loading dose for the placebo arm consists of 2 injections, each containing placebo formulation in a 2 mL volume, administered at day 1 and followed by qw injections of 2 mL placebo formulation from week 1 through week 15 (last dose of study drug will be at week 15).
Endpoint(s)	During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries.
Primary:	• Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
Co-Primary for European Union (EU) and EU Reference Market Countries:	• Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 • Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

Secondary:	**Key Secondary Endpoints:** • Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EU and EU reference market countries as it is already a co-primary endpoint) • Percent change from baseline to week 16 in Pruritus Numerical Rating Scale (NRS) • Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16 **Other Secondary Endpoints:** • Percent change in EASI score from baseline to week 16 • Change from baseline to week 16 in percent Body Surface Area (BSA) • Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD) • Percent change from baseline to week 16 in Global Individual Signs Score (GISS) (erythema, infiltration/population, excoriations, lichenification) • Change from baseline to week 16 in Dermatology Life Quality Index (DLQI) • Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM) • Change from baseline to week 16 in Hospital Anxiety Depression Scale (HADS) • Percent change from baseline to week 2 in pruritus NRS • Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16 • Incidence of treatment-emergent adverse events (TEAEs) leading to treatment discontinuation from baseline through week 16 • Overall incidence of TEAEs through week 16 • Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
Procedures and Assessments	A variety of parameters will be collected during the study to assess the efficacy of dupilumab, including measures of AD severity, and patient-reported measures of AD symptoms and quality of life (QOL). The safety of dupilumab in this population will be assessed by evaluating TEAEs, detailed medical history, thorough physical examination, vital signs, electrocardiograms (ECGs), and clinical laboratory testing. Concomitant

	medications and procedures will be collected from time of informed consent to the end of the study. Safety data will be reviewed on an ongoing basis by the sponsor. An independent data monitoring committee (IDMC) that oversees the entire dupilumab clinical development program will review safety data periodically in an unblinded fashion and will advise the sponsor of potential safety signals. Blood samples will be collected for dupilumab concentration and anti-dupilumab antibody (ADA) levels at pre-determined time points. Research samples and samples for exploratory biomarker analysis will be collected.
Statistical Plan	**Sample Size:** To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total with a randomization ratio of 1:1:1 dupilumab, 300 mg qw: 300 mg q2w: placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment) to detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively. The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively. The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. **Efficacy Analysis Set:** The full analysis set (FAS) includes all randomized patients. Efficacy analysis will be based on treatment allocated at randomization (as randomized), which will be stratified by disease severity and region. The per protocol set (PPS) includes all patient 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. The criteria of major protocol deviations are defined as the following:

- A patient who does not receive treatment as randomized
- Any major violations of efficacy-related entry criteria
- The percentage of a patient's compliance with study drug injection is <80% or >120% of the scheduled doses during the study treatment period

Methods:

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

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

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.

Primary Efficacy Analysis

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

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, different analysis methods will be used:

- For US and US reference market countries: Missing data from the randomized population will be imputed multiple times to generate a complete dataset at each imputation by using the multiple imputation (MI) Statistical Analysis Software (SAS) procedure with Markov Monte Carlo algorithm. These complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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.
- For EU and EU reference market countries: A mixed-effect model with repeated measures (MMRM) will be used. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary time point, week 16, as well as at the other time points by time point-specific contrasts

from the MMRM model.

For the binary efficacy endpoints, if rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used. If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal.

For the continuous efficacy endpoints, if a patient receives rescue medication, the data collected after rescue medication is initiated will be treated as missing.

Sensitivity analysis using other missing data handling approaches will also be performed.

Multiplicity Considerations

For US and US reference market countries: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For the comparison of each dose regimen with placebo, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section of secondary endpoints.

For EU and EU reference market countries: The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one. The hierarchy for the secondary endpoints is shown in the section on section endpoints.

Safety Analysis: Will be based on the SAF. This includes TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and ECG results). A summary of safety results for each treatment group will be presented.

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Appendix 1. Factors to Consider in Assessing the Relationship of AEs to Study Drug

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of covariance
Anti-dsDNA	Anti-nuclear antibody against double-stranded DNA
Anti-TPO	Anti-thyroid peroxidase antibody
ARGUS	A Pharmacovigilance and Risk Management Safety Software System
AST	Aspartate Aminotransferase
BSA	Body surface area of involvement of atopic dermatitis
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFNγ	Interferon gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin

IL-4Rα	Interleukin-4 receptor alpha
IRB	Institutional Review Board
ISR	Injection site reactions
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
NRS	Numerical Rating Scale
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term
QOL	Quality of life
qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
TARC	Thymus and activation-regulated chemokine (CCL-17)
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (ie, itchiness), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD (Bieber 2008).

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction.

Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE) - and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, hypothalamic pituitary axis effects, Cushing's disease, etc.). Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants (Schmitt 2007) and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation.

Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids (Schmitt 2009, Schram 2012, Akhavan 2008). Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

Up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents (Hart 2002, Wenzel 2007).

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. This population includes patients who are often treated with systemic corticosteroids, as well as other non-selective immunosuppressants, including cyclosporine, which are associated with significant toxicities. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. As of the cut-off date (28 March, 2014), there has been no evidence in the ongoing phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab for up to 12 weeks.

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 is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients 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). This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab.

1.2.2. Rationale for Dose Selection

The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). All patients randomized to receive treatment with dupilumab will get an initial loading dose of 600 mg on day 1. 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.

The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021), which evaluated dupilumab dose regimens of 300 mg qw, 300 mg q2w, 300 mg every 4 weeks (q4w), 200 mg q2w, and 100 mg q4w, versus placebo, administered for 16 weeks. An interim analysis was conducted after 240 patients completed 12 weeks of treatment. The interim analysis, which focused primarily on week 12 outcomes, indicated that dupilumab 100 mg q4w had suboptimal efficacy, whereas the 300 mg qw dupilumab regimen demonstrated the highest efficacy and was comparable to other dupilumab dosing regimens with respect to safety parameters. Therefore, the 300 mg qw dose was selected for further evaluation in phase 3 together with a 300 mg dose administered less frequently, q2w. Both doses were selected to be evaluated in this study to further refine the understanding of dose-response relationships in a larger sample of study patients and to explore a dose regimen with less frequent administration.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients 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 confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study (see below).

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened 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 (emollients) at least twice daily for at least the 7 consecutive days immediately 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 non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 1:1:1 ratio to receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by region (details will be specified in the interactive voice response system/interactive web response system [IVRS/IWRS] specifications document). Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks (Figure 1). Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Table 1 and Table 2).

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

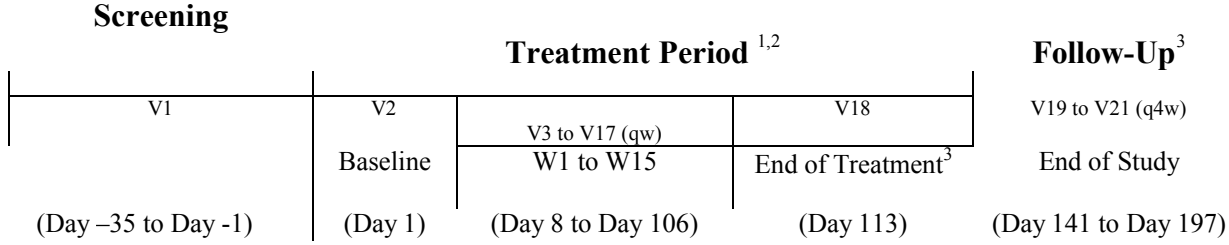
Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in a maintenance study. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study, but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Patients with an ADA titer of ≥240 at their last study visit and some patients who are negative for ADA at their last study visit will be asked to return to the clinic to have additional ADA samples collected for analysis (see section 6.3.4.2 for details and time points).

Figure 1: Study Flow Diagram



[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered.

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

3.2. Planned Interim Analysis

No interim analysis is planned.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An independent data monitoring committee (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 is 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 600 patients will be enrolled at approximately 160 global sites.

4.2. Study Population

The study population consists of adults 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).

4.2.1. Inclusion Criteria

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

1. Male or female, 18 years or older
2. Chronic AD, (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]), that has been present for at least 3 years before the screening visit
3. EASI score ≥16 at the screening and baseline visits
4. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits
5. ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits
6. Baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥3

   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. Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks

   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 (±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 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 re-screened after such documentation is obtained (ie, patients are shown to fail a 28-day course of mid-to-higher potency TCS [±TCI]).

8. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (NOTE: See exclusion criterion #6 for limitations regarding emollients). (See background treatment with topical emollient in section 5.2.)
9. Willing and able to comply with all clinic visits and study-related procedures
10. Able to understand and complete study-related questionnaires
11. Provide signed informed consent

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 an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
3. 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:
   - Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
   - Phototherapy for AD
4. Treatment with TCS or TCI within 1 week before the baseline visit

5. Treatment with biologics as follows:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte count returns to normal, whichever is longer
    - Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer
6. 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)
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit
8. Planned or anticipated use of any prohibited medications (see section 5.7.1) and procedures during study treatment
9. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: patients may be rescreened after infection resolves
11. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per investigator judgment
12. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
13. Positive with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at the screening visit
14. At baseline, presence of any conditions listed as criteria for study drug discontinuation (see section 5.4.2)
15. Presence of skin comorbidities that may interfere with study assessments
16. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
17. 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
18. History of alcohol or drug abuse within 2 years of the screening visit

19. 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 (HbA1c ≥ 9%), patients with cardiovascular conditions (eg, stage 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 [CRFs], etc.)
20. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may 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, CRFs, etc.)
21. Planned or anticipated major surgical procedure during the patient's participation in this study
22. Patient is a member of the investigational team or his/her immediate family
23. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
24. Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 120 days after last dose of study drug. These include hormonal contraceptives, intrauterine device, or double barrier contraception (ie, condom + diaphragm) or a 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

*For females, menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone level of ≥25 mU/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception.

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 investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, adverse event (AE), treatment failure, protocol violation, cure, and for

administrative, or other reasons. An excessive rate of withdrawals would diminish the informative value of the study data; therefore, unnecessary withdrawal of patients should be avoided. Patients who discontinue study treatment but who consent to remain in the study will continue to comply with study visits and assessments.

Patients who withdraw prematurely from the study will be asked to complete study assessments per section 6.2.5.

See section 3.1 for details of the maintenance and OLE studies.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

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

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

Patients will receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or weekly injections of matching placebo (following a placebo "loading dose") during the 16-week treatment period.

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 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 3 and 4 (weeks 1 and 2, respectively) and all other visits in the clinic. 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], 3 [day 8], and 4 [day 15]) and blood pressure and heart rate determined. The patient (or caregiver) will administer study drug outside of the clinic during weeks in which no clinic visit is scheduled.

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

The procedure for preparing the dupilumab dose for SC injection will be provided in the pharmacy manual. Subcutaneous injection sites 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 (ISRs), study drug should be administered only into areas of

normal-looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual.

Detailed instructions for transport, storage, preparation, and administration of study drug will be provided by the site to the patient (or caregiver). Patients will complete a dosing diary to document compliance with self-injection of study drug outside 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 and to continue 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 non-lesional 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.

5.3. Rescue Treatment(s)

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. For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication. All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

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 temporarily or 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 and complete all study assessments per the study schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per section 6.2.5.

5.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Evidence of pregnancy
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3x upper limit of normal (ULN) with total bilirubin >2x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5x 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).

- Other reasons that may lead to the permanent discontinuation of study treatment include:
  - Treatment with any prohibited concomitant medication or procedure (section 5.7.1)

5.4.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.0 \times 10^3/\mu L$ but $>0.5 \times 10^3/\mu L$
  - Platelet count $\leq 100 \times 10^3/\mu L$ but $>50 \times 10^3/\mu L$
  - Creatine phosphokinase (CPK) >10x ULN
- Other intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (eg, cyclosporine, methotrexate, azathioprine, mycophenalate-mofetil, Janus kinase inhibitors, biologic agents, etc)

After the lab abnormality leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. Similarly, study treatment may resume after the medication leading to suspension of dosing is discontinued. 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 600 patients will be randomized on day 1 in a 1:1:1 ratio to receive qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo for 16 weeks. Patients will be randomized to a treatment group according to a central randomization scheme provided by an IVRS/IWRS to the designated site personnel or clinical staff members. Randomization will be stratified by disease severity (IGA 3 vs IGA 4) and region (details will be specified in the IVRS/IWRS specifications document and will be documented in the clinical study report).

5.5.1. Blinding

With the exception of the statistician who provides the randomization sequence, the IDMC statistician, the IDMC members, and the provisions in section 5.5.2, this study will remain blinded to all individuals until the pre-specified 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 weekly

injections of dupilumab or placebo starting at day 1. During weeks in which dupilumab is not administered in the q2w dosing regimen, patients will receive placebo.

Anti-drug antibody and drug concentration results will not be communicated to the sites, and the sponsor 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 the treatment assignment for a patient may be necessary due to a medical emergency, a serious adverse event (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). Details for emergency unblinding will be provided in the study manual.

- 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 at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2°C to 8°C 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

Any treatment administered from the time of informed consent 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:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

NOTE: If a patient receives treatment with systemic corticosteroids or other systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures

- Phototherapy
- Tanning in a bed/booth

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.

5.7.2.1. Cytochrome P450

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized.

However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (Abdel-Razzak 1993, Christensen 2012). Human peripheral blood mononuclear cells incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (Liptrott 2009).

Limited in vitro findings suggest that IL-4 and IL-13 may affect CYP levels and potentially activities. However, the clinical significance of these data is not fully understood. During the study treatment and at least up to the end of follow-up, investigators are cautioned to monitor clinical and laboratory signs that might indicate a potential drug-drug interaction in all patients receiving dupilumab concomitantly with narrow therapeutic index medications that are metabolized by CYP (see Investigator's Brochure for more details of such drugs). This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal, if needed.

For more details, refer to the study manual.

5.7.2.2. Prohibited Concomitant Medications or Procedures as Rescue

If medically necessary (eg, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator (see section 5.3 for details).

Blinded adjudication of concomitant medications may be performed to identify concomitant medications that confound study endpoints.

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 and Table 2.

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

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												
Safety:[7]														
Weight	X	X												
Height	X													
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV Ab, HBsAg, HBcAb, Hep C Ab, TB[11]	X													
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[12]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[13]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

[1] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

[2] For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

[3] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[4] Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[5] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[6] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[7] To be collected before the injection of study drug.

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

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

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

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites.

Table 2: Schedule of Events – (Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination)

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6,7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Total serum IgE				X	X	X	X	X	X
Antigen-specific IgE samples[11]				X			X	X	X
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[12]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[13]				X			X	X	X

[1] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

[2] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required

[3] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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

[4] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[5] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[6] To be collected before the injection of study drug.

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

[8] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

[11] Includes: antigen-specific IgE (region-specific allergen panels).

[12] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites

[13] Patients with an ADA titer of ≥240 at the last study visit will be asked to return to the clinic to have additional samples collected for analysis (see section 6.3.4.2 for details and time points).

6.2. Study Visit Descriptions

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

1. Patient Reported Outcomes.
2. Investigator assessments (performed only by adequately trained investigators or sub-investigators; the same investigator or sub-investigator should perform all the evaluations for a given patient throughout the entire study period).
3. Safety and laboratory assessments.
4. Administration of study drug.

6.2.1. Visit 1/Screening/Day –35 to Day -1

After the patient has provided informed consent, the following information will be collected:

- Informed consent for optional assessments (for patients who consent to participate in the genomic sub-study)
- Inclusion/exclusion
- Medical history and concurrent illnesses
- Demographics
- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Training on IVRS
- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - Patient Oriented Eczema Measure (POEM)
  - Hospital Anxiety and Depression Scale (HADS)
  - Dermatology Life Quality Index (DLQI)
  - European Quality of Life-5 Dimensions (EQ-5D)
  - Asthma Control Questionnaire (ACQ-5)
  - Sinonasal Outcome Test (SNOT-22)
- Patient Global Assessment of Disease
- Vital signs
- Investigator's Global Assessment (IGA)

- Eczema Area and Severity Index (EASI)
- Global Individual Signs Score (GISS)
- SCORing Atopic Dermatitis (SCORAD)
- Body Surface Area of (BSA) involvement of atopic dermatitis
- Weight
- Height
- Physical examination
- Electrocardiogram (ECG)
- Laboratory testing:
  - HIV antibody
  - HBsAg
  - HBcAb
  - Hepatitis C antibody
  - TB testing (on a country-by-country basis)
  - Hematology and Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - Thymus activation-regulated chemokine (TARC)
  - Total serum IgE
  - Antigen-specific IgE (region-specific allergen panels)
  - Highly sensitive C-reactive protein (hs-CRP)
  - Anti-nuclear antibody (ANA)
  - Anti-double-stranded DNA (anti-dsDNA)
  - Anti-thyroid peroxidase (anti-TPO)
  - Skin microbiome samples (select sites)
  - Research samples

6.2.2. Treatment Period

6.2.2.1. Visit 2/Baseline/Day 1

The following information will be collected:

- Inclusion/Exclusion

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology and Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP

  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - DNA and RNA samples
  - Functional dupilumab pharmacokinetic (PK) sample
  - Anti-dupilumab antibody sample
- Randomization
- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.2. Visit 3/Week 1/Day 8 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Vital signs
- IGA
- EASI
- GISS
- SCORAD

- BSA
- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

6.2.2.3. Visit 4/Week2/Day 15 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample

- Administer study drug after all the other assessments have been performed. Train patient/caregiver in injection technique.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection: in addition to the pre-dose assessments, vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection
- Provide patient dosing diary
- Study drug dispensation

6.2.2.4. Visit 5/Week 3/Day 22 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.5. Visit 6/Week 4/Day 29 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment

- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.6. Visit 7/Week 5/Day 36 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.7. Visit 8/ Week 6/Day 43 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.8. Visit 9/Week 7/Day 50 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS

- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.9. Visit 10/ Week 8/Day 57 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE

  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.10. Visit 11/Week 9/Day 64 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.11. Visit 12/Week 10/Day 71 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug.
- Complete dosing diary (for patients who receive study drug outside the study center

6.2.2.12. Visit 13/Week 11/Day 78 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.13. Visit 14/Week 12/Day 85 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD

- BSA
- Laboratory testing:
  - Hematology, Chemistry
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
- Administer study drug. Observe patient/caregiver technique
- Check patient dosing diary
- Study drug dispensation/accountability

6.2.2.14. Visit 15/Week 13/Day 92 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.15. Visit 16/Week 14/Day 99 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administer study drug.
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.16. Visit 17/Week 15/Day 106 (±3 days)

This visit may be conducted by telephone for patients electing to self-administer study drug.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administer study drug
- Complete dosing diary (for patients who receive study drug outside the study center)

6.2.2.17. Visit 18/End of Treatment/Week 16/Day 113 (±3 days)

The end of treatment at week 16 (visit 18) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment

- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.3. Follow-up Period

6.2.3.1. Visit 19/Week 20/Day 141 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.3.2. Visit 20/Week 24/Day 169 (±3 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Laboratory testing:
  - TARC
  - Total serum IgE

6.2.4. Visit 21/End of Study Visit/Week 28/Day 197 (±3 days)

The end of study at week 28 (visit 21) will be for those patients who decline to enter the OLE or maintenance study.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale

- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient global assessment of disease
- Patient global assessment of treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA

- Anti-TPO
- Skin microbiome samples (select sites)
- Research samples
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

6.2.5. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 16) will be asked to return to the clinic for 2 visits: once for early termination assessments, and again at week 16 (primary endpoint visit), as described in section 6.2.2.17. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS

- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA
  - Anti-dsDNA
  - Anti-TPO
  - Skin microbiome samples (select sites)
  - Research samples
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Check patient dosing diary
- Study drug accountability

6.2.6. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. During an unscheduled visit, any of the procedures noted may be performed, but not all are required.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus categorical scale
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - HADS
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- GISS
- SCORAD
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology, Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - TARC
  - Total serum IgE
  - Antigen-specific IgE
  - hs-CRP
  - ANA

- Anti-dsDNA
- Anti-TPO
- Skin microbiome samples (select sites)
- Research samples
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

Assessments performed only at the screening and/or baseline visit include: medical history, medication history, demographics, diagnosis of chronic AD, HBsAg, HBcAb, anti-HIV antibody, and hepatitis C antibody. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

6.3.2. 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 will be administered only to the subset of patients who fluently speak a language in which the assessment tool has been translated. These 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 POEM, HADS, DLQI, and EQ-5D).

6.3.2.1. Patient Assessment of Pruritus

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average 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 overall (on average) during the previous 24 hours?"
- 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS

items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.2. Patient-Assessed Pruritus Categorical Scale

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in 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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

6.3.2.3. 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 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 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 6.2.

The POEM is provided in the study reference manual.

6.3.2.4. 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 6.2.

The HADS is provided in the study reference manual.

6.3.2.5. Patient-Reported Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL (Badia 1999). The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which

assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. 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 6.2.

The DLQI is provided in the study reference manual.

6.3.2.6. Patient-Assessed EQ-5D

The EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement (ie, no problems, some problems, or severe problems) in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

The EQVAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)". This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

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 6.2.

The EQ-5D is provided in the study reference manual.

6.3.2.7. Patient Global Assessment of Disease

Patients will rate their overall wellbeing based on a 5-point Likert scale from poor to excellent. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent." Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.8. Patient Global Assessment of Treatment

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent". Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.9. Juniper Asthma Control Questionnaire

The 5-question version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.10. Sinonasal Outcome Test

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) 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 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.11. Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at time points according to section 6.2.

The assessment tool is provided in the study reference manual.

6.3.2.12. 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 6.2.

The IGA is provided in the study reference manual.

6.3.2.13. 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 6.2.

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

6.3.2.14. Body Surface Area Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 6.2.

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

6.3.2.15. 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. The GISS will be assessed at time points according to section 6.2.

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

6.3.2.16. SCORing Atopic Dermatitis

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). There are 3 components to the assessment: A = extent or affected body surface area, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see section 6.3.2.14) 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, 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 VAS, 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 6.2.

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

6.3.2.17. 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 (pre-dose). Subsequent photographs of the same area will be taken at week 16 (end of treatment) and week 28 (end of study).

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

6.3.3. Safety Procedures

6.3.3.1. Physical Examination

A thorough and complete physical examination will be performed at time points according to section 6.2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

6.3.3.2. Weight and Height

Weight and height will be determined at time points according to section 6.2.

6.3.3.3. Vital Signs

Vital signs, including heart rate, blood pressure, body temperature, and respiration rate, will be collected pre-dose at time points according to section 6.2. Vital signs (blood pressure and heart rate) will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation.

6.3.3.4. Electrocardiogram

Electrocardiograms will be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to section 6.2. The ECG strips or reports will be retained with the source documentation, and the results will be documented in the electronic case report form.

Electrocardiogram results will be interpreted by a central reading center. Instructions for performing the assessment and transmitting ECG data are provided in the central ECG reference manual.

6.3.3.5. Laboratory Testing

Hematology, chemistry, urinalysis, and serum pregnancy testing samples will be analyzed by a central laboratory. The urine pregnancy test kit will be provided to the site by the laboratory.

Blood samples for serum chemistry and hematology testing will be collected to measure overall patient health at screening. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory. 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 6.2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[1]

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be reflexly measured when CPK >5X 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

Microscopic analysis will only be done in the event of abnormal dipstick results.

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

Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at time points according to section 6.2.

Testing for HIV antibody, HBsAg, HBcAb, and hepatitis C antibody will be performed at screening. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

Abnormal Laboratory Values and Laboratory Adverse Events

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

- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in section 7.2.5.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Samples for dupilumab concentration will be collected at time points listed in section 6.2.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in section 6.2.

Patients with an ADA titer of ≥240 at their last study visit (early termination or end of study) will be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months, until their titers fall below 240. Some patients who are negative for ADA at their last study visit will also be asked to return to the clinic within 6 to 12 months from their last dose of study drug to have additional ADA samples collected to maintain the blind.

6.3.5. Research Testing

Research assessments are performed for exploratory purposes only; results for assessments in the sub-sections below will not be reported in the clinical study report. Results will be reported separately from the clinical study report.

6.3.5.1. Research Samples

Research samples (serum/plasma) will be collected at time points according to section 6.2.

Use and Storage of Research Samples (Serum/Plasma)

Research serum and plasma samples will be collected to study the effects of the study drug on modulation of the IL-4 receptor and on atopic disease processes, as well as to study biomarkers that may have predictive utility for response to dupilumab treatment. Unused samples collected for drug concentration or ADA analyses may also be used for other research purposes. Remaining samples may be stored (up to 10 years) for future use in experiments related to AD or related diseases. If necessary, the samples may also be used to identify markers associated with toxicity.

6.3.5.2. Genomics Sub-Study - Optional

Patients will be asked to participate in an optional genomics sub-study. Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study informed consent form (ICF) before collection of the samples. Blood for DNA extraction should be collected on day 1/baseline (pre-dose), but may be collected at any study visit. RNA samples

will be collected at time points according to section 6.2. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA and RNA samples for the genomics sub-study will be double-coded as defined by the ICH guideline E15. Sub-study samples may be stored for up to 10 years after the final date of the clinical study report and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to IL-4/13 pathway inhibition (via IL-4Rα blockade), atopic disease risk, prognosis and progression, or other clinical outcome measures. These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Genome-wide studies, including (but not limited to) single nucleotide polymorphism analyses and genomic sequencing may also be performed. If indicated, genomic analyses may also be performed to identify markers associated with toxicity.

6.3.5.3. Exploratory Biomarker Testing

Biomarkers to be analyzed in this study are: TARC, total serum IgE, antigen-specific IgE (region-specific, allergen-specific panels), *S. aureus* enterotoxin A-specific IgE, *S. aureus* enterotoxin B-specific IgE, hs-CRP, ANA, anti dsDNA, anti-TPO. Skin swab samples for skin microbiome testing may be banked. Samples will be collected at time points according to section 6.2. These are exploratory assessments to further the understanding of AD-associated biomarkers and the response to dupilumab treatment. The results of these tests will not be used to evaluate patient eligibility for study participation.

Thymus and activation regulated chemokine and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug. These results may also 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, and will be evaluated as an exploratory marker of efficacy. These markers may also be assessed for their potential value in predicting treatment response.

Staphylococcus aureus colonization and infection on the skin is a significant complication for many AD patients. To determine whether or not dupilumab treatment can reduce colonization and/or infection, exploratory samples for skin microbiome analyses may be banked. Non-invasive skin swab samples from lesional and non-lesional skin may be collected to characterize the skin microbiome diversity and *S. aureus* abundance. Skin swab samples for culturing (eg, semi-quantitative analysis of methicillin-sensitive and methicillin-resistant *S. aureus* colonization) may also be collected.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs 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 also be tested for predictive utility.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an

increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti-dsDNA, anti-TPO, and ANA) will be measured.

Detailed instructions for sample collection are provided in the laboratory manual.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

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

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

7.1.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as 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).

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 16 weeks 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 in this study include:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Severe ISRs that last longer than 24 hours
- Mycosis fungoides or other forms of cutaneous T cell lymphoma
- Any severe infection; any infection requiring treatment with parenteral antibiotics/anti-viral/anti-fungal agent; any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks; any clinical endoparasitosis; any opportunistic infection

Note: Generally, all uncommon, atypical, peculiar, or unusually persistent infections, especially viral infections, should be reported as AESIs.

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.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

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

Is there a reasonable possibility that the adverse event was 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

A list of factors to consider in assessing the relationship of AES to study, see Appendix 1.

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, AD history and characteristics, and medication history.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoint

During discussions with health authorities, different health authorities requested different primary endpoints although the conduct of the study will be the same for all countries. As a result:

The primary endpoint is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Union (EU) and EU reference market countries only, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

8.2.2. Secondary Endpoints

The key secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EU and EU reference market countries as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16

Other secondary endpoints are:

- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD

- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of treatment-emergent adverse events (TEAEs) leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16

8.2.3. Other Endpoints and Assessments

- Absolute and percent change from baseline to week 16 in: EQ-5D, Patient Global Assessment of Disease and Patient Global Assessment of Treatment
- Distribution of disease severity scores (eg, IGA, EASI, SCORAD) and their change from baseline
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Absolute and percent changes in efficacy parameters through week 16
- Characterization of dupilumab serum concentrations through week 16
- Correlation analyses:
  - Body weight vs serum concentrations
  - Serum concentrations vs clinical outcomes
  - Body weight vs clinical outcomes
  - Association between baseline biomarkers (eg, TARC, total IgE) and clinical response
- Incidence of dupilumab ADA

8.3. Pharmacokinetic Variables

The PK variables may include, but are not limited to, the following:

- C_{trough} over time
- C_{last}
- T_{last}
- Time to steady state
- $C_{troughSS}$ - steady state trough concentration

8.4. Anti-drug Antibody Variables

ADA variables include status (positive or negative) and titer as follows:

- Total positive at any time
- Pre-existing immunoreactivity - a positive ADA response at baseline
- Treatment emergent - defined as either any positive response when baseline results are negative, or if any post treatment ADA response is ≥4-fold over baseline titer levels
- Persistently positive
- Transiently positive
- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

If a sample tests positive for ADA, the neutralizing activity of the ADA will be assessed.

9. STATISTICAL PLAN

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

Analysis variables are listed in section 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

Disease severity and region 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

To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size will be increased to 600 in total with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo.

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 by the IVRS/IWRS at randomization (as randomized).

The per protocol set (PPS) includes all patient 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. The criteria of major protocol deviations are defined as the following:

- A patient who does not receive treatment as randomized
- Any major violations of efficacy-related entry criteria
- The percentage of a patient's compliance with study drug injection is <80% or >120% of the scheduled doses during the study treatment period

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). If a patient receives a dose regimen different to that assigned during the study, this patient will be considered as treated by the lowest active dose regimen. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

9.3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all randomized patients with at least 1 post-baseline drug concentration result.

9.3.4. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all randomized patients with at least 1 post-baseline ADA result.

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, median, standard deviation, 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. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

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 (region, disease severity) will be used for the percentage of patients with IGA 0 or 1 at week 16 or percentage of patients with EASI-75 at week 16.

To account for the impact of rescue medication on the efficacy effect:

For the binary efficacy endpoints, if rescue medication is used (see section 5.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.

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

Sensitivity analysis using 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.

In addition, the Cochran-Mantel-Haenszel method adjusted by randomization strata will also be performed on the observed variable regardless of rescue medication use and missing values.

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, different analysis methods will be used:

- For US and US reference market countries: Missing data from the randomized population will be imputed multiple times to generate a complete dataset at each imputation by using the multiple imputation (MI) Statistical Analysis Software (SAS) procedure with Markov Monte Carlo algorithm. These complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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.
- For EU and EU reference market countries: A mixed-effect model with repeated measures (MMRM) will be used, which will account for the missing data. This model includes the factors (fixed effects) for treatment, randomization strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. The MMRM model will provide baseline adjusted least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p-values for treatment comparisons by the appropriate time point-specific contrasts from the model. Additional details on the MMRM model will be provided in the SAP.

To account for the impact of rescue medication on the efficacy effect:

- Continuous efficacy endpoints: if a patient receives rescue medication that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue medication is initiated will be treated as missing.
- If a patient withdraws from the study, this patient will be counted as a non-responder for binary endpoints after withdrawal.

In addition to the MMRM model or the MI method described previously, sensitivity analysis using LOCF and MMRM/MI methods (if one of them is not described as the main analysis) will be conducted. Robustness of the MMRM model to departure from the missing-at-random

assumption will be explored using sensitivity analysis based on the pattern mixture model. Additional details on these sensitivity analyses will be provided in the SAP.

9.5.2.3. Multiplicity Considerations

For US and US reference market countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

For EU and EU reference market countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients achieving EASI-75 (≥75% reduction from baseline in EASI score at week 16 (this is not a secondary endpoint for the EU and EU reference market countries as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in pruritus NRS
- Incidence of TESAEs from baseline through week 16

- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

9.5.3. Safety Analysis

Safety analysis will be based on the SAF. This includes reported TEAEs and other safety information (ie, 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 pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug (day 1) to the end of the study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing 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 patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

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

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

9.5.3.2. Other Safety

Vital Signs

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

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.

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

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for 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 and calculated as:

(Date of last study drug injection – date of first study drug injection) + 7 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:

Treatment Compliance =

(Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) x 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

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

9.5.5. Analysis of Anti-Drug Antibody Data

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

9.5.6. Analysis of Quality of Life Data

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

9.5.7. 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-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 non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given

visit, the first observation will be used in summaries and all observations will be presented in listings.

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

The CRF data for this study will be collected with an electronic data capture 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, study drug supply
- EDC system – data capture/uploading and storing photographs
- Statistical Analysis Software (SAS) – statistical review and analysis
- ARGUS – a PVRM Safety System
- nQuery Advisor – sample size calculations

11. STUDY MONITORING

11.1. Monitoring of Study Sites

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

concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

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

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

11.3. Case Report Form Requirements

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

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

12. AUDITS AND INSPECTIONS

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

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

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

the clinical study or its supporting activities both within and outside of the investigator's institution.

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

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

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) must be kept in strict confidence.

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

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

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS dated 05 Feb 2015, and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

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

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

No:

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

Yes:

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

NOTE: This list is not exhaustive.

STATISTICAL ANALYSIS PLAN

Title: A phase 3 confirmatory study investigating the efficacy and safety of dupilumab Monotherapy administered to adult patients with moderate-to-severe atopic dermatitis

Protocol: R668-AD-1416

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

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List of abbreviations and definition of terms

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BAS	Biomarker analysis set
BSA	Body surface area
BUN	Blood urea nitrogen
CRF	Case report form
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonisation
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed effect model with repeated measures
NRS	Numerical rating scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term

qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

1 OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of this study. The SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for R668-AD-1416 study.

This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. These revisions will be based on blinded review of the study and data.

1.1 Background and Rationale

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus, xerosis, and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD.

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction. Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption. Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated

application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation. Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids. Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

IL-4 and IL-13 have been implicated as an important inflammatory component. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents.

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. There has been no evidence in the phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab.

This is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable. This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021).

1.2 Study Objectives

1.2.1 Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

1.2.2 Secondary Objectives

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD.

1.2.3 Modifications from the Statistical Section in the Final Protocol

Modifications from the Amended protocol 2 on Analyses of Secondary Efficacy Variables

- Multiple Imputation (MI) is used as the primary analysis method for continuous variables. MMRM will be used as a sensitivity analysis method for continuous variables. Sensitivity analysis by pattern mixture model will not be performed.
- Add the endpoint "Proportion of patients with improvement (reduction) of pruritus NRS ≥4 from baseline to week 16" as a key secondary endpoint
- Change the order of the hierarchy for the secondary endpoints, i.e. move the endpoint "Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16" prior to the endpoint of "Incidence of TESAEs from baseline through week 16".

2 INVESTIGATIONAL PLAN

2.1 Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study is either 16 weeks (16-week treatment period) or 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study. Eligible patients will be randomized in a 1:1:1 ratio to qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by country.

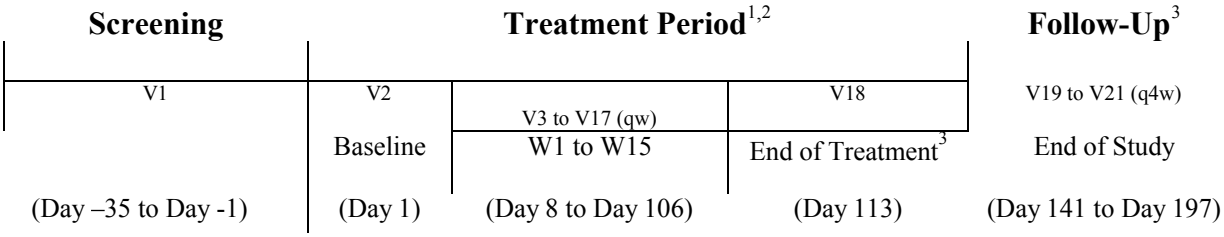
2.2 Sample Size and Power Considerations

To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size was increased to 600 in total with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. Power calculation was implemented by nQuery Advisor 7.0.

2.3 Study Plan

The study consists of a screening period, a treatment period and a follow-up period as presented below:



[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out. Patients may be re-screened 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 at least twice daily for at least the 7 consecutive days immediately before randomization and continue throughout the study. To allow adequate assessment of skin dryness, moisturizers should not be applied on the areas of non-lesional skin used for such assessments for at least 8 hours before the clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab

concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Appendix 10.2).

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in the maintenance study, R668-AD-1415. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study (R668-AD-1225), but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

Patients with an ADA titer of ≥240 at their last study visit and some patients who are negative for ADA at their last study visit may be asked to return to the clinic to have additional ADA samples collected for analysis. See section 4.7 for details.

3 ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following population of analysis will be used for all statistical analysis.

3.1 Efficacy Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). This is the primary analysis population for efficacy analysis.

Patient who was randomized more than once will be analyzed as distinct patients based on the treatment allocated at randomization.

Patients who temporarily or 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 and complete all study assessments per the study schedule.

3.2 Per Protocol Analysis Set

The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations.

A major efficacy-related protocol violation is one that may affect the interpretation of study results. The criteria of major efficacy-related protocol deviation are defined as following:

- Patients who did not receive treatment as randomized, which are defined as
  - patients on placebo but accidentally exposed to dupilumab,
  - patients on dupilumab receiving > 2 injections different from planned treatment
- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
  - Inclusion criteria 3, 4, 5 and 6
  - Exclusion criteria 3 ,4, 5, 6, 7 and 8
- Patients who received <80% or >120% of the scheduled doses during the study treatment period

The PPS will be finalized before the database lock.

3.3 The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive any study drug, and will be analyzed as treated.

The actual treatment group is defined following rules below:

- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen group

- For patients on dupilumab accidentally receiving ≤ 2 vials different from the planned treatment, the actual treatment group allocation for as-treated analysis will be the planned dupilumab dose / regimen
- For patients on dupilumab receiving > 2 vials different from planned treatment, the actual treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen group

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized

The safety analysis will be based on the SAF.

3.4 The Pharmacokinetic Analysis Set (PKAS)

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.

3.5 The ADA Analysis Set (AAS)

The ADA population will consist of all treated patients who received any study drug and who had at least one qualified ADA result after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

4 ANALYSIS VARIABLES

4.1 Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age at screening (year), age group (<65, >=65), Sex, Ethnicity, Race, Region (Americas, Asia Pacific, East Europe, West Europe), Country, Baseline Weight (kg), Height (m), and BMI (kg/m^2)
- Baseline characteristics: Duration of AD disease, Pruritus numerical rating scale (NRS) for maximum or average itch intensity, Pruritus categorical scale, Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, Global Individual Signs Score (GISS), SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) Involvement of Atopic Dermatitis, Patient global assessment of disease status, Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Itchy Quality of Life (QoL), EQ-5D and Hospital Anxiety and Depression Scale (HADS), Asthma Control Questionnaire (ACQ-5), and Sinonasal Outcomes Test (SNOT-22)

4.2 Medical History and Atopic Disease Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO. Information on conditions related to AD includes diagnosis of AD and AD treatment history, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy hives and other allergies due to medications, animals, plants, mold, dust mites, etc. Recent AD history within 1 year before the screening visit is also collected with information of number of AD flares and episodes of skin infections requiring pharmacological treatment.

4.3 Pre-treatment / Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the EOS visit.

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

Prohibited concomitant medications/procedures: Treatment with the following concomitant medications is prohibited during the study:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

Rescue treatments (medications/procedures): 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.

Patients who receive rescue treatment during the study treatment period will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment.

If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) study treatment will be immediately discontinued.

After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure.

4.4 Efficacy Variables

4.4.1 Primary Efficacy Variable

During discussions with health authorities, different health authorities requested different primary endpoints, although the conduct of the study will be the same for all countries. As a result, the primary endpoint for US and US reference market countries is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Union (EU) and EU reference market countries, as well as Japan, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument to rate AD disease severity globally in clinical studies. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration. IGA score will be assessed at every scheduled and unscheduled clinic visit.

Eczema Area and Severity Index (EASI)

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 score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section.

The EASI will be collected at every scheduled and unscheduled clinic visit.

4.4.2 Secondary Efficacy Variables

The key secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA EU and EU reference market countries, as well as Japan as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16

Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average 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 overall (on average) during the previous 24 hours?"
- 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

For each day, if there are multiple NRS of the same question (average or worst) scores collected on a same day, take average of all the scores collected.

The baseline NRS is defined as the prorated average of the NRSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline NRS, The mean weekly NRS is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3. The baseline NRS and mean weekly NRS will be calculated for average itch intensity and peak itch intensity separately.

Other secondary efficacy endpoints are:

- Percent change in EASI score from baseline to week 16
- Proportion of patients with EASI-90 at week 16
- Change from baseline to week 16 in percent BSA
- Change from baseline to week 16 in SCORAD
- Percent change from baseline to week 16 in GISS

- Percent change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in weekly average of peak daily pruritus NRS
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 every scheduled and unscheduled clinic visit.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). The extent of AD is assessed by the Investigator as a percentage of each defined body area 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 (erythema, oedema / papulation, excoriations, lichenification, oozing / crusts and dryness) of AD is assessed by the Investigator 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 (VAS), 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. The maximum SCORAD score is 103.

Patients will undergo this assessment at every scheduled and unscheduled clinic visit.

Global Individual Signs Score (GISS)

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally by the Investigator (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe) using the EASI severity grading criteria. The cumulative score is the sum of the four components, which will be ranged from 0 to 12. The GISS will be assessed at every scheduled and unscheduled clinic visit.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire (Badia 1999) used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on Quality of Life (QoL). The format is a simple response to 10 items, which assess QoL over the past week. For each item, the scale is rated as follows: 0='not at all'='not relevant'; 1='a little'; 2='a lot'; 3='very much'='yes' in question 7, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. The DLQI will be assessed at every scheduled and unscheduled clinic visit.

- Handling missing items from DLQI

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
ii. If two or more questions are left unanswered the questionnaire is not scored.
iii. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
iv. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
v. If two or more response options are ticked for one question, the response option with the highest score should be recorded.
vi. The DLQI can be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

Hospital Anxiety and Depression Scale (HADS)

The HADS is a general Likert scale used to detect states of anxiety and depression (Bjelland 2002). The 14 items on the questionnaire include 7 that are related to anxiety (odd number questions) and 7 that are related to depression (even number questions). Each item on the questionnaire is scored from 0 (the best) to 3 (the worst) according to the content of the item; a person can score between 0 and 21 for either anxiety or depression. A high score is indicative of a poor state. For each sub-scale: if one question is missing, 7 times the prorated mean of the remaining six questions is imputed. If more than one question is missing, then the subscale is missing. The total score is the sum of two sub-scores. HADS will be assessed at every scheduled and unscheduled clinic visit.

Patient Oriented Eczema Measure (POEM)

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 patient response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping). Each item is a 5-point scale (from 0='no days' to 4='every day'). The total score is the sum of the 7 items which is ranged from 0 to 28 and reflects disease-related morbidity; a high score is indicative of a poor QOL. The POEM will be assessed at every scheduled and unscheduled clinic visit.

DLQI, HADS and POEM will be administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

4.4.3 Other Efficacy Variables

Other efficacy variables include:

- Change and percent change from baseline to week 16 in: EQ-5D, Patient Global Assessment of Disease and Patient Global Assessment of Treatment
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Change and percent changes in efficacy parameters through week 16

Pruritus Categorical Scale (PCS)

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in clinical studies of AD and has less of a "middling" effect (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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

For each day, if there are multiple PCS scores collected on the same day, the maximum (worst) of all the scores collected will be chosen. For each week, calculate round prorated average of collected scores for Category Score. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3 round to 1.0.

The baseline PCS is defined as the round prorated average of the PCSs reported continuously for 7 days right before the baseline visit.

Patient Global Assessment of Disease Status

Patients will rate their overall wellbeing based on a 5-point Likert scale. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing". Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5). Patients will undergo this assessment at the following visits: screening, day 1/baseline

(pre-dose), and days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

Patient Global Assessment of Treatment Effect

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5). Patients will undergo this assessment at the following visits: days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

EQ-5D

The EQ-5D is a standardized measure of health status developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economic appraisal (Greiner 2005). The EQ-5D as a measure of health related QOL, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health."

The 5 dimensional 3-level systems are converted into a single index utility score. Values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model and weighted according to the social preferences of the UK population. The minimum value for the single index utility score is –0.594, The EuroQol Visual Analogue Scale (EQVAS) records the respondent's self-rated health on a vertical visual analogue scale. The VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcomes as judged by the individual respondents. EQ-5D self-reported VAS data generates information on the self-perceived overall health-related quality of life. Appendix 10.4 provides the SAS code to derive the index utility score using UK based population. EQ-5D will be assessed at every scheduled and unscheduled clinic visit.

EQ-5D will be administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

4.5 Safety Variables

4.5.1 Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, latest version).

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally

associated with the use of a medicinal product, whether or not considered related to the medicinal (investigational) product.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

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

The pre-treatment period is defined as the period from the subject providing informed consent up to the first dose of study drug. The treatment and follow-up period is defined as the period from the administration of first study dose to the EOS visit.

The pre-treatment AE and treatment emergent AE (TEAE) are defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during pre-treatment period.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered as TEAEs.

4.5.2 Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Blood samples for serum chemistry and hematology testing will be collected at screening (day -35 to day -1), baseline (day 1), on days 29, 57, 85, 113, 197 (EOS) or ET, and at unscheduled visits. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory.

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[1]

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be reflexly measured when CPK >5X the ULN

Hematology with Differential

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

Urinalysis

Urine samples for urinalysis will be collected to measure overall patient health at screening, and will also be collected at (day -28 to day -1), baseline (day 1), on days 113, 197 (EOS) or ET, and at unscheduled visits.

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

Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Evidence of pregnancy
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5 \times 10^3$ μL
  - Platelet count $\leq 50 \times 10^3$ μL

- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3x upper limit of normal (ULN) with total bilirubin >2x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
- Confirmed AST and/or ALT >5x ULN (for more than 2 weeks)

- Other reasons that may lead to the permanent discontinuation of study treatment include: treatment with any prohibited concomitant medication or procedure

Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.0 \times 10^3/\mu L$ but $>0.5 \times 10^3/\mu L$
  - Platelet count $\leq 100 \times 10^3/\mu L$ but $>50 \times 10^3/\mu L$
  - Creatine phosphokinase (CPK) >10x ULN
- Other intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (eg, cyclosporine, methotrexate, azathioprine, mycophenalate-mofetil, Janus kinase inhibitors, biologic agents, etc)

4.5.3 Vital Sign Variables

The following vital signs parameters will be collected:

- Weight (kg) and height (cm)
- Respiratory rate (bpm)
- Heart rate (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (^oC)

Weight is determined at screening and day 1/baseline, and days 113, 197 (EOS), any unscheduled visit, or ET. Height is only measure at screening. Other vital signs are collected pre-dose at every scheduled and unscheduled clinic visit. Blood pressure and heart rate will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation.

4.5.4 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] $=QT/[RR^{0.33}]$ and QTc Bazett [QTcB]$=QT/[RR^{0.5}]$) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at screening, days 113 and 197 (EOS) or ET.

4.5.5 Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.

A thorough and complete physical examination will be performed at screening, day 113, and day 197 (EOS) or ET.

4.6 Pharmacokinetic (PK) Variables

- Characterization of functional dupilumab concentrations in through week 16
- Correlation analyses:
  - Body weight vs functional dupilumab concentrations
  - Functional dupilumab concentrations vs clinical outcomes

Samples for drug concentration will be collected at day 1/baseline (pre-dose), days 15, 29, 57, 85, 113, 197 (EOS), unscheduled visits and ET. Pharmacokinetic variables may include but not limited to C_{trough} over time, $C_{last,}$ $T_{last,}$ time to steady state and $C_{troughSS}$ (steady state trough concentration).

4.7 Antibody (ADA) Variable

Serum samples for anti-dupilumab antibody assessment will be collected at day 1/baseline and at days 15, 29, 57, 113, and 197 (EOS), unscheduled visits and ET.

Incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by active treatment groups. Listing of all ADA titer levels will be provided for patients positive in the ADA assay.

ADA variables include ADA status (positive or negative) and titer as follows:

- Total subjects negative in the ADA assay at all times
- Total subjects positive in the ADA assay at any time.
- Total subjects with preexisting immunoreactivity
  - Pre-existing immunoreactivity- defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.
- Subjects with treatment emergent response in the ADA assay (ADA Incidence)
  - Treatment emergent - defined as either a positive response in the ADA assay post first dose when baseline results are negative, OR if any post first dose positive response in the ADA assay is greater than or equal to 4-fold over baseline titer levels. The treatment emergent responses will be further characterized into Persistent and Transient
  - Persistent Response- Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by at least a 12-week period OR the last collected samples is positive in the ADA assay
  - Transient Response- Any treatment emergent ADA positive response that is not considered persistent.
- Titer Values (Titer value category)
  - Low (titer <1,000)

- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

ADA positive samples will be further characterized for the presence of neutralizing antibody responses.

Patients with an ADA titer of ≥240 at their last study visit (early termination or end of study) may be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months, until their titers fall below 240. Some patients who are negative for ADA at their last study visit may also be asked to return to the clinic within 6 to 12 months from their last dose of study drug to have additional ADA samples collected to maintain the blind.

4.8 Other Variables (QoLs and Biomarkers)

Juniper Asthma Control Questionnaire (ACQ-5)

The 5-question version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of asthma and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment). A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ, any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing value, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

Sinonasal Outcome Test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

It contains 22 items. The total score of the SNOT-22 is calculated by summation of all the item scores. The total score ranges from 0 to 110. The MCID is equal to 8.9. For patients where some SNOT-22 items were incomplete, a total score for the SNOT-22 will be imputed as mean of the completed items, providing at least 50% of items have been completed. If more than 50% of items are missing, the total score will be considered as missing.

Twenty two items are classified into five domains as in following table. The score for each domain is the sum of response to each question in that domain. Domain score will be imputed as mean of the completed items in that domain, providing at least 50% of items in that domain have been completed.

Domain	Items
Nasal	2, 3, 4, 6, 7, 12
Ear	8, 9, 10
Sleep	13, 14, 15, 16
General and practical	1, 5, 11, 17, 18, 19
Emotional	20, 21, 22

Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at day 1/baseline, days 29, 57, 85, 113, 141, 169, 197 (EOS), unscheduled visits and ET.

Biomarker: Association between baseline biomarkers (eg, TARC, total IgE) and clinical response

Biomarkers to be analyzed in this study are:

- TARC and total serum IgE
- antigen-specific IgE
- hs-CRP, ANA, anti dsDNA, anti-TPO

TARC and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs in circulation, indicating they are atopic. To further understand atopy in this patient population, region-specific, allergen-specific IgE panels will be performed.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti-dsDNA, anti-TPO, and ANA) will be measured.

Samples will be collected at time points according to the schedule in 10.2.

5 STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

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

5.1 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups based on FAS. Listing of demographics and baseline characteristics will be presented.

5.2 Medical and AD History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

Medical history will be listed, sorted by treatment groups based on the SAF.

5.3 Pre-treatment/Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications/procedures, prohibited medications/procedures and rescue medications/procedures will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined dupilumab treatment groups.

Listing of pre-treatment medication and concomitant medications will include generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, route.

The detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized by topical and systemic groups. Kaplan Meier curves for time to first rescue use will be generated.

The compliance of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group.

5.4 Subject Disposition

The following summaries by table will be provided:

- The total number of screened patients
- 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 treatment and the reasons for the discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation

The following listings will be provided:

- Listing of subject disposition including: date of randomization, date of the last visit, received dose, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized, including the patients who missed active study drug doses to the point that their cumulative exposure ends up being closer to another study regimen that is different from the one to which they had been randomized (e.g., a patient randomized to 300 mg qw who missed 30-50% of doses will be closer to 300 mg q2w than to the originally assigned 300 mg qw)
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation, summary tables of reasons will be provided
- Summary table with listing of protocol deviations will be provided

5.5 Dose administration

The compliance with protocol-defined investigational product will be calculated as follows:

Treatment Compliance= (Number of injections during exposure period) / (Number of planned injections during exposure period) x 100%

Loading doses for the same patient will be counted as 1.

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information, and whether or not the total dose is administered for each dose will be presented.

If subjects received treatment different from the randomized treatment or stopped treatment due to an AE, or overdosed, the listings will be provided.

5.6 Treatment Exposure and Observation Period

The duration of treatment exposure period during the study is calculated as:

(Date of last study drug injection – date of first study drug injection) + 7

regardless of unplanned intermittent discontinuations. The duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums.

The duration of observation period during the study is calculated as:

(Date of the last visit – date of the first study medication dose) +1.

The number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest is specified as:

≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 43 days, ≥50 days, ≥ 57 days, ≥ 64days, ≥ 71 days, ≥ 78 days, ≥ 85 days, ≥99 days, ≥113 days, ≥127 days, ≥141 days, ≥155 days, ≥169 days, ≥183 days, ≥197 days.

5.7 Analyses of Efficacy Variables

For all efficacy variables, the analysis will be comparisons of each dupilumab regimen and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested for each dupilumab regimen group and the placebo group:

H0: $p_{dupilumab} = p_{placebo}$, where p stands for the percent of responders in a treatment group

H1: $p_{dupilumab} \neq p_{placebo}$.

The analyses of efficacy variables are summarized in Appendix 10.1.

5.7.1 Analysis of Primary Efficacy Variable

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

Handling of dropouts or adjudicated rescue medication or missing value for the binary response variables

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

To account for the impact of rescue medication on the efficacy effect:

For the binary efficacy endpoints, if rescue medication is used (see section 4.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.

If the patient has the missing value at week 16, then it will be counted as a non-responder at week 16.

Sensitivity analysis

1. Last observation carried forward (LOCF) approach after censoring for rescue medication use or study withdrawal 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.

2. All observed data, no matter if rescue medication is used or data is collected after withdrawal will be included for the primary endpoint. Patients with missing value will be counted as non-responder.

3. Same as the main statistical analysis but including only patients in PPS.

Subgroup analyses

Subgroup analyses will be performed for the primary efficacy variable by:

- Baseline disease severity [moderate (IGA=3) and severe (IGA=4) AD]

- Region/country
- Baseline body weight (< overall median, >= overall median)
- Age (<65, 65-75 and >75)
- Gender
- Ethnicity
- Race
- Baseline EASI (>30, <=30)
- Baseline peak NRS (<7, >=7)
- Duration of AD (<overall median, >=overall median)
- Previous usage of cyclosporine (Yes, No)
- History of asthma (Yes, No)
- History of nasal polys (Yes, No)

5.7.2 Analyses of Secondary Efficacy Variables

The binary secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoints.

The endpoint "Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16" will only be analyzed for patients with baseline peak pruritus NRS ≥4.

The continuous endpoints will be analyzed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model. Missing data from the FAS will be imputed 50 times to generate 50 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. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.
>
> Step 2. The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, randomization strata (region, disease severity), and relevant baseline.

The week 16 data of each of the 50 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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 50 analyses using Rubin's formula.

Patients' efficacy data through week 16 after the rescue medication usage will be set to missing first, and then be imputed by the multiple imputation method.

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, the baseline value and the randomization strata
- Measured endpoint values from every clinic visit up to week 16

Categorical variables included in above model (i.e., treatment group and randomization strata) are not expected to be missing.

To account for the impact of rescue medication on the efficacy effect:

- Continuous efficacy endpoints: if a patient receives rescue medication that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue medication is initiated will be treated as missing.

Sensitivity analysis

In addition to the MI method described previously, sensitivity analyses for the continuous endpoints for EASI and/or Pruritus NRS will be conducted as described below.

1. The sensitivity analysis based on all observed data no matter if rescue medication is used or data is collected after withdrawal using MI method will be performed.
2. This sensitivity analysis will use a mixed-effect model repeated measures (MMRM). The model will include factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within-patient errors. Denominator degrees of freedom will be estimated using approximation of SATTERTH. The efficacy data will be set to missing after rescue medication is used. Afterwards no imputation will be made.

   The MMRM model will provide least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error, confidence interval, and the p-value for treatment comparisons. The graph of LS-mean +/- se by visit will be provided.
3. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue medication is used. The LOCF method will then be used to impute missing values.

Analysis of incidence of TEAE-related variables

- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

These endpoints will be analyzed for patient in SAF. The period from baseline through week 16 is defined as from study day 1 to study day 113. The Cochran-Mantel-Haenszel test adjusted for randomization strata (region, disease severity) will be used for the percentage of patients with events described above through week 16.

In addition, a negative binomial regression model will be used to assess treatment differences in number of events described above. The model will include the total number of events as response

variable, and treatment group and randomization strata as covariates. Log-transformed observation duration will be the offset variable.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and placebo will be derived by testing each active dose group versus placebo separately. Two-sided 95% confidence intervals of the rate ratio will be provided. The estimated events rate and its 2-sided confidence intervals will be provided for each treatment group.

Multiplicity Considerations

For US and US reference market countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

For EU and EU reference market countries, as well as Japan:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients achieving EASI-75 (≥75% reduction from baseline in EASI score at week 16 (this is not a secondary endpoint for the EU and EU reference market countries, as well as Japan as it is already a co-primary endpoint)
- Percent change from baseline to week 16 in pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16
- Percent change in EASI score from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 2 in pruritus NRS

- Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16
- Incidence of TESAEs from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16
- Overall incidence of TEAEs through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

5.7.3 Analyses of Other Efficacy Variables

Analyses of categorical variables will be similar to the primary analysis; analyses of continuous variables similar to the secondary analyses.

In addition, the following endpoints will be analyzed:

- Number (%) of patients with HADS-A or HADS-D >=8 at week 16
- Number (%) of patients with HADS-A or HADS-D >=11, at week 16
- Number (%) of patients with HADS-A or HADS-D >=8 at week 16 for those patients with HADS-A or HADS-D >=8, or HADS-A or HADS-D >=11, at baseline
- Number (%) of patients with HADS-A or HADS-D >=11 at week 16 for those patients with HADS-A or HADS-D >=11, at baseline

5.8 Analysis of Safety Data

The summary of safety and tolerance will be performed based on SAF.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs, and 12-lead ECG.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables, vital signs and ECG are defined in Appendix 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

5.8.1 Adverse Events

Listings of Pre-treatment AEs, TEAEs and serious TEAEs will be generated.

The following variables will be included in the listing:

- Patient id
- Treatment group
- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)

- Verbatim Term
- AE start date and end date/ongoing (using both calendar days and study days)
- AE Duration
- Relationship of AE to study drug: unrelated or related
- Action taken: Dose withdrawn temporarily, Dose reduced, Dose withdrawn permanently, Dose not changed, Not known or Not applicable
- Severity: using a 3–point scale (mild, moderate, or severe)
- Treatment: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with sequelae, recovering/ resolving, not recovered/not resolved, fatal or unknown

Listing of TEAEs resulting in death and study discontinuation will also be generated

Number and proportions of subjects reporting TEAEs will be summarized, sorted by decreasing frequency of SOC and PT for the highest dose level.

Summaries of TEAEs will include:

- Proportion of subjects with at least one TEAEs
- Proportions of subjects with at least one TEAEs by SOC/PT
- Proportions of subjects with at least one TEAEs by SOC/HLT/PT
- Proportions of subjects with at least one TEAEs by PT
- Proportion of subjects with at least one TEAEs by severity by SOC/PT
- Proportion of subjects with at least one TEAEs related to study medication by SOC/PT
- Proportion of subjects with at least one serious TEAEs by SOC/PT
- Proportion of subjects with TEAEs leading to discontinuation of study treatment by SOC/PT

Summary of the most frequent (>=5%) TEAEs by SOC, HLT, PT, respectively, in the aggregate dupilumab groups and in the overall study population will be provided.

SAEs/AESI during treatment and follow up period will be listed.

5.8.2 Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with abnormal lab value during study whose screening and baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs during study, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by subject and visit will be provided.

5.8.3 Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings will be provided with flags indicating the treatment-emergent PCSVs, depending on data.

5.8.4 Physical Exams

The number (n) and percentage (%) of subjects with abnormal physical exams will be summarized at baseline, end of treatment period and end of study by treatment group. A summary of treatment-emergent abnormal findings will be provided.

5.8.5 Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings will be provided with flags indicating PCSVs, depending on data.

5.9 Analysis of Pharmacokinetic Data

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

5.10 Analysis of ADA Data

The ADA variables will be analyzed using descriptive statistics. Drug concentration data will be examined and the potential influence of ADAs on concentration-time profiles will be evaluated. Assessment of impact of ADA on safety and efficacy will be provided.

5.11 Analysis of Other Variables (QoLs and Biomarkers)

Changes or percentage changes from baseline to each measurement visit in ACQ-5 and SNOT-22 will be summarized. Number of sick Leave/missed school days from each assessment will be summarized by treatment group.

Descriptive statistics for the observed values, change from baseline and percent change from baseline values by treatment and visit will be provided for the following biomarker variables:

- TARC (screening, days 1, 15, 29, 57, 85, 113, 197)
- total serum IgE (screening, days 1, 29, 57, 85, 113, 141, 169, 197)
- antigen-specific IgE (screening, days 1, 29, 57, 85, 113, 197)
- hs-CRP, ANA, anti dsDNA, anti-TPO (screening, days 1, 57, 85, 113, 197)

The Wilcoxon signed-rank test will be used to test if the change or percentage change from baseline value is significantly different from zero. P-value will be reported.

Exploratory analyses for the difference between dupilumab groups and placebo on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group as fixed effects, and the relevant baseline values as covariate. Missing value will be imputed by LOCF method for visits between post-baseline to visit 18 (week 16). After visit 18, no imputation will be made. P-value for difference from placebo will be provided.

Correlation of baseline TARC (measured value), IgE (measured value), and positivity to at least one antigen-specific IgE with the following clinical endpoints will be explored using the Spearman's rho tests. Both Spearman correlation coefficients and p-value will be reported from the model.

- IGA 0-1 at week 16
- EASI-75 at week 16
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS $\geq$3 from baseline to week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD

Shift tables from baselines status to post-baseline status for hs-CRP, ANA, anti dsDNA and anti-TPO variables will be provided by treatment group.

All above analyses will be performed on the FAS for

- All observed data, no matter if rescue medication is used or data is collected after withdrawal
- All observed data with censoring after rescue medication use or study withdrawal.

6 DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1 Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of NRS is defined in section 4.2.

6.2 General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3 Data Handling Convention Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAE. For example, if the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as "related" in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to in line with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of follow up date. Imputation flag is 'Y'.

6.4 Analysis Visit Window

All available values obtained between 2 planned visits including unscheduled measurements will be pooled to the analysis visit window according to the following definition:

Visit	Target Day	Analysis Time Window
Screening (1)	<1	<1
Day 1 (Baseline, 2)	1	1
Right after Baseline (3)	d_3	[2, flooring((d_3 + d_4+1)/2)]
…	….	…
i (i>3)	d_i	…
i+1	d_{i+1}	(ceiling((d_i + d_{i+1})/2), flooring((d_{i+1} + d_{i+2}+1)/2)]
i+2	d_{i+2}	…
…	….	…
Last	D_{last}	(ceiling((d_{last-1} + d_{last})/2), flooring((3d_{last} - d_{last-1})/2)]

In the event of multiple measurements of the same test in the same window, if the measurements are from different categories, the priority order is ET, scheduled then unscheduled visit. For the measurements in the same category, the value measured nearest to the target day will be assigned to the window; if they are at the same distance to the target day, the latest one will be used. Laboratory, vital sign and ECG data collected from unscheduled visits will be used in PCSV analysis, and will be pooled into analysis window for the by visit analysis. The above analysis-window algorithm applies also to the efficacy endpoints.

For the ePRO data collected daily via IVRS, the analysis visit windows will be implemented following the procedures below:

Step 1: Derive the study day,

If diary date >= 1st injection date, diary study day=diary date – 1st injection date +1; Otherwise diary study day=diary date – 1st injection date

Step 2: Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc.

7 INTERIM ANALYSIS

No interim analysis is planned.

8 SOFTWARE

All analyses will be done using SAS Version 9.2 or above.

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10 APPENDIX

10.1 Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16;	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Secondary continuous variables	FAS	MI	MMRM, ANCOVA with LOCF	Yes for EASI and NRS endpoints	Line plot
Categorical variables	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test / LOCF	Yes for EASI and NRS endpoints	Histogram

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2 Schedule of Events

Screening, Baseline, and Treatment Period

Study Procedure	Screening	Baseline	Treatment Period											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)			**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)	**-35 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												
Safety:[7]														
Weight	X	X												
Height	X													

Study Procedure	**Screening**	**Baseline**	**Treatment Period**											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)	**-35 to -1**	**D1**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)			**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV Ab, HBsAg, HBcAb, Hep C Ab, TB[11]	X													
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[12]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[13]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

[1] The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

[2] For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

[3] Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[4] Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[5] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[6] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[7] To be collected before the injection of study drug.

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

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

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

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites.

Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6, 7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X
Total serum IgE				X	X	X	X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Antigen-specific IgE samples[11]				X			X	X	X
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[12]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[13]				X			X	X	X

1 The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

2 During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.

3 The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

4 For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

5 Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

6 To be collected before the injection of study drug.

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

8 Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

9 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

10 Select sites only - photograph AD area

11 Includes: antigen-specific IgE (region-specific allergen panels).

12 Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites

13 Patients with an ADA titer of ≥240 at the last study visit will be asked to return to the clinic to have additional samples collected for analysis

10.3 Criteria for Treatment-Emergent Potentially Clinical Significant Value

Parameter	PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(>35% Total Bilirubin **and** TBILI>1.5 ULN), and baseline (Total Bilirubin <=35% **or** TBILI <=1.5 ULN)	Conjugated bilirubin dosed on a case-by-case basis.

Parameter	PCSV	Comments
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L ≥30% to < 100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Creatinine Clearance (Cokcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 -<30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 - < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 - < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Use is optional. FDA draft guidance 2010 Four independent criteria, will provide additional shift table if needed
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hyponatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.

Parameter	PCSV	Comments
Lipasemia	≥3 ULN and < 3ULN at baseline	
Amylasemia	≥3 ULN and < 3ULN at baseline	
Glucose		
Hypoglycaemia Hyperglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA May 2005. ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent

Parameter	PCSV	Comments
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	

Parameter	PCSV	Comments
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSV to be identified in individual subjects/patients listings. 5 independent criteria

10.4 SAS code for EQ-5D index utility scoring

```
/*=================================================================*/;
/*  Aim                      : Derive the EQ5-D index (utility)
*/;
/*  Source for the algorithm : scoring EQ-5D health states (Rosalind
Rabin */;
/*            (cf. G:\_HE\PRO
questionnaire\EQ5D\scoring\YorkTariffx.doc)  */;
/*  Note                     : UK based population (Dolan, 1997)
*/;
/*  Author                   : Elisheva Smadja
*/;
/*=================================================================*/;

data EUROQOL;   set temp;
   profil=
(10000*eqq1cd)+(1000*eqq2cd)+(100*eqq3cd)+(10*eqq4cd)+eqq5cd;
   eq5d=1;
**********Mobility*********;
if eqq1cd=2     then eq5d=eq5d-0.069;
if eqq1cd=3     then eq5d=eq5d-0.314;
********Self-care**********;
if eqq2cd=2     then eq5d=eq5d-0.104;
if eqq2cd=3     then eq5d=eq5d-0.214;
******Usual activities*****;
if eqq3cd=2     then eq5d=eq5d-0.036;
if eqq3cd=3     then eq5d=eq5d-0.094;
*****Pain/discomfort******;
if eqq4cd=2     then eq5d=eq5d-0.123;
if eqq4cd=3     then eq5d=eq5d-0.386;
*****Anxiety/depression*****;
if eqq5cd=2     then eq5d=eq5d-0.071;
if eqq5cd=3     then eq5d=eq5d-0.236;

if (eqq1cd ne 1 or eqq2cd ne 1 or eqq3cd ne 1 or eqq4cd ne 1 or eqq5cd
ne 1)
                then eq5d=eq5d-0.081;
if (eqq1cd=3 or eqq2cd=3 or eqq3cd=3 or eqq4cd=3 or eqq5cd=3)
                then eq5d=eq5d-0.269;
if (eqq1cd=. or eqq2cd=. or eqq3cd=. or eqq4cd=. or eqq5cd=.)
                then eq5d=.;
run;
```

Title: A phase 3 confirmatory study investigating the efficacy and safety of dupilumab Monotherapy administered to adult patients with moderate-to-severe atopic dermatitis

Protocol: R668-AD-1416

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BAS	Biomarker analysis set
BSA	Body surface area
BUN	Blood urea nitrogen
CRF	Case report form
EAIR	The exposure-adjusted incidence rate
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonisation
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed effect model with repeated measures
NEPY	Number of events per 100 patient-years
NRS	Numerical rating scale

PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PRC	Protocol review committee
PT	Preferred term
qw	Weekly
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of this study. The SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for R668-AD-1416 study.

This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. These revisions will be based on blinded review of the study and data. This plan will be finalized prior to the final database lock.

1.1. Background and Rationale

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus, xerosis, and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD.

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics and skin barrier dysfunction. Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption. Topical calcineurin inhibitors (TCI) are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated

application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation. Cyclosporine, a current therapy for severe AD in some regions, is a potent immunosuppressant affecting both humoral and cellular immune responses. This results in increased susceptibility to infections and decreased cancer immunosurveillance. Other commonly recognized toxicities include hypertension and impaired renal and hepatic function. In addition, cyclosporine interacts with other commonly used medicines potentially affecting their metabolism and effect. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids. Biological agents including anti-tumor necrosis factor (TNF) α (infliximab, etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti CD11a (efalizumab) have generally been ineffective in clinical trials. Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

IL-4 and IL-13 have been implicated as an important inflammatory component. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. Inhibition of this Th2 inflammatory pathway is currently being and has previously been evaluated with other agents.

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate–to-severe AD. In many cases, treatment benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects. There has been no evidence in the phase 2b dose-ranging study or, in all studies completed thus far, of increased risk of serious infections during treatment with dupilumab.

This is a phase 3, randomized, double-blind, placebo-controlled efficacy and safety study conducted in patients with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable. This study will generate information regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg weekly (qw) or 300 mg every 2 weeks (q2w). The doses of dupilumab in this study were based on the efficacy and safety results from a phase 2b dose-ranging study (R668-AD-1021).

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

1.2.2. Secondary Objectives

The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

1.3. Modifications from the Statistical Plan in the Final Protocol

Modifications from the Amended protocol 2 (final protocol) on Analyses of Secondary Efficacy Variables

- Multiple Imputation (MI) is used as the primary analysis method for continuous variables. MMRM will be used as a sensitivity analysis method for continuous variables. Sensitivity analysis by pattern mixture model will not be performed.
- Add the endpoints "Proportion of patients with improvement (reduction) of pruritus NRS ≥4 from baseline to week 16, to week 4 and to week 2, respectively" as key secondary endpoints
- Change the order of the hierarchy for the secondary endpoints, i.e. move the endpoint "Incidence of skin infection TEAE requiring systemic treatment from baseline through week 16" prior to the endpoint of "Incidence of TESAEs from baseline through week 16"

Modifications from the Amended protocol 2 on concomitant medication/procedure

Any concomitant treatment is considered from the first dose of study medication in the SAP instead of the time of informed consent in the protocol

1.4. Modifications from the Previously Approved SAP

Item	Section	Changes/Updates Description	Rationale
1	2.1	Randomization strata: 'country' changed to 'region'	Correction
2	2.3	Removed the paragraph of ADA titer	Clarification
3	3.2	Updated the timing of PPS determination	Clarification
4	3.3	Added two analysis period for safety analysis	Clarification
5	3.4	Updated the description of PK analysis set	Clarification
6	4.1	Updated Demographic and baseline characteristics variables	Per clinical request
		Add the patient with inadequate response to topicals (Yes/NO)	Per UK/Ireland HA request
7	4.2	Updated the version of MedDRA	Clarification
8	4.4.2	Updated key and other efficacy endpoints	In response to FDA's

Item	Section	Changes/Updates Description	Rationale
			comment
9	4.4.2	Updated introduction of HADS and POEM	Clarification
10	4.4.3	Updated introduction of EQ-5D and added some variables from section 4.8	Clarification
11	4.5.2	Removed the irrelevant description	Clarification
12	4.7	Updated introduction of ADA variables	Clarification
13	4.8	Updated introduction of ACQ-5, removed some variables other than biomarkers to section 4.4.3 and re-titled	Clarification
14	5.4	Added Number of patients who entered into follow-up period	Clarification
15	5.6	Updated the days cutoffs for the duration of treatment and duration of the observation period	Clarification
16	5.7	Updated the subgroup analyses	In response to comments from FDA and EMA
		Change the thread value for SCORAD subgroup	Per clinical request
17	5.7.2	Added WOCF to the sensitivity analyses	In response to FDA's comment
18	5.7.2	Updated the hierarchy of the secondary endpoints	Clarification
19	5.7.3	Updated the analysis of other efficacy endpoints	Clarification
20	5.8.1	Updated TEAE incidence	Per clinical request
21	5.8.1	Added NEPY, EAIR and associated analyses	Per clinical request
22	5.8.1	Added AESI	Per clinical request
23	5.10	Updated ADA algorithms	Clarification
24	5.11	Updated biomarker analyses	Clarification
25	6.1	Updated definition of baseline measurements	Clarification
26	6.3	Updated missing data handling rules	Clarification
27	6.4	Updated analysis visit windowing algorithm	Clarification
28	10.5	Added AESI search criteria	In response to FDA’s comments

2. INVESTIGATIONAL PLAN

2.1. Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study duration is between 16 weeks (16-week treatment period) and 28 weeks (16-week treatment period and 12-week follow-up), depending on whether or not patients continue in a maintenance or extension study. Eligible patients will be randomized in a 1:1:1 ratio to qw SC injections of 300 mg dupilumab, q2w SC injections of 300 mg dupilumab, or matching placebo. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] vs. severe [IGA 4]) and by regions (Asia Pacific, East Europe, North and South America and West Europe).

2.2. Sample Size and Power Considerations

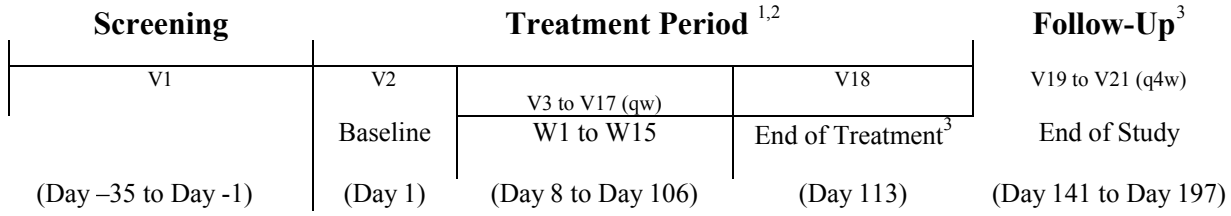
To detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming that the percentages are 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power is 55 per group. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the maintenance study, the sample size was increased to 600 in total with a randomization ratio of 1:1:1 dupilumab 300 mg qw:300 mg q2w:placebo. It is estimated that with 200 patients per group, the study can provide 99% power in both comparisons (between dupilumab 300 mg qw and placebo treatment and between dupilumab 300 mg q2w and placebo treatment, respectively). The same numbers of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 responder at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

The significance level is set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups with placebo. Power calculation was implemented by nQuery Advisor 7.0.

Additional power calculation based on the secondary endpoint "proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16": As the analysis includes patients with baseline peak pruritus NRS ≥4, assumed that 180 such patients are randomized into each treatment group, with responder rates 39% and 9% for dupilumab and placebo respectively, the analysis can provide 99% power at 0.025 level from each comparison.

2.3. Study Plan

The study consists of a screening period, a treatment period and a follow-up period as presented below:



[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered.

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.

[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out. Patients may be re-screened 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 at least twice daily for at least the 7 consecutive days immediately before randomization and continue throughout the study. To allow adequate assessment of skin dryness, moisturizers should not be applied on the areas of non-lesional skin used for such assessments for at least 8 hours before the clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized receive qw SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (during weeks in which dupilumab is not administered, patients will receive placebo), or matching placebo (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 each week from day 1 to week 15. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose, study treatment will be administered weekly for the subsequent 15 weeks. Patients will have the option to self-administer study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visit 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.

During the 16-week treatment period, patients will have weekly study visits (some visits may be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Appendix 10.2). ADA samples collected at day 1 (baseline) at Week 16 (EOT), at Week 28 (EOS), and at early termination (ET) will be analyzed for ADA. In response to AE's of special interest like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgement of the medical investigator and/or medical monitor.

The end of treatment visit will occur at week 16, 1 week after the last dose of study drug. The primary endpoint will be determined at week 16.

Patients with IGA 0 to 1 or eczema area severity index (EASI)-75 at week 16 who have not received rescue treatment for AD will be eligible to participate in the maintenance study, R668-AD-1415. Patients who meet these criteria, but choose not to participate in the maintenance study may be eligible to participate in an open label extension (OLE) study (R668-AD-1225), but no sooner than 36 weeks after completing the week 16 visit in the current study. Patients who do not meet eligibility criteria for the maintenance study will undergo at least 4 weeks follow-up (through week 20). At week 20:

- patients with IGA 3 to 4 may be eligible to enroll in a subsequent OLE study in which they will receive treatment with dupilumab
- patients with IGA <3 will continue follow-up to week 28 or until their IGA becomes 3 or 4 (whichever comes first)

For patients who decline participation in the OLE or maintenance study, follow-up visits will occur every 4 weeks from week 20 through week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 28.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations of analysis will be used for all statistical analyses.

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). This is the primary analysis population for efficacy analyses.

Patient who was randomized more than once will be analyzed as distinct patients based on the treatment allocated at the initial randomization and will be analyzed separately.

Patients who temporarily or 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 and complete all study assessments per the study schedule.

3.2. Per Protocol Analysis Set

The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations.

A major efficacy-related protocol violation is one that may affect the interpretation of study efficacy results. The criteria of major efficacy-related protocol deviation are defined as following:

- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
  - Inclusion criteria 3, 4, 5 and 6
  - Exclusion criteria 3 ,4, 5, 6, 7 and 8
- Patients who received <80% or >120% of the scheduled doses during the study treatment period

Final determination of the PPS will be made in the blinded manner prior to the database lock.

3.3. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive any study drug, and will be analyzed as treated.

The actual treatment group is defined by the following rules:

- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen
- For patients on dupilumab accidentally receiving ≤ 2 injections different from the planned treatment, the actual treatment group allocation for as-treated analysis will be the planned dupilumab dose / regimen
- For patients on dupilumab receiving > 2 injections different from planned treatment, the actual treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose / regimen

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized

The safety analyses will be based on the SAF.

For safety summaries, three analysis periods are defined as follows:

- Week 16 treatment period is defined as
  - Day 1 to the study completion date of the week 16 visit (113 days starting from the first dose of study drug if the date of the week 16 treatment visit is unavailable) for those patients who entered the maintenance study (R668-AD-1415) which is defined as having the "Transition into another study R668-AD-1415 SOLO-CONTINUE study" on the CRF Study Completion Status page checked
  - Day 1 to the week 16 visit date or early termination date, whichever comes first, for those patients who did not enter the maintenance study (R668-AD-1415)
- Follow-up period is defined as the date after the week 16 visit date (113 days starting from the first dose of study drug if the date of Week 16 treatment visit is unavailable) to the date of the end of study visit
- Overall study Period is defined as day 1 to the date of the end of study visit, consisting of both the treatment and follow-up periods

The SAF will be the basis for the analyses for the week 16 treatment period and overall study period; however, for the analyses for the follow-up period, only a subset of SAF will be included, which is defined as the patients who entered the follow-up period and had at least one visit after week 16 treatment visit.

3.4. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set includes all randomized patients who received any study drug and who had at least one qualified PK sample result following the first dose of study drug up to Week 16, and will be analyzed as the treated groups defined in the SAF.

The PKAS will be applied for the PK analysis according to the separately documented PK analysis plan.

3.5. The ADA Analysis Set (AAS)

The ADA population will consist of all treated patients who received any study drug and who had at least one reportable ADA result (either “ADA negative” or “ADA positive”) after first dose of the study drug.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age at screening with grouping (year; ≥18-<40, ≥40-<65, ≥65), Sex, Ethnicity with grouping (Hispanic or Latino, Not-Hispanic or Latino), Race with grouping (White, Black, Asian, Other), Region (for global submission: Americas, Asia Pacific, East Europe, West Europe, Country, Baseline weight with grouping (kg, <70; ≥70-<100, ≥100), Height (m), and BMI (kg/m^2; <15, ≥15-<25,

≥25-<30, ≥30), Patients with inadequate response to topicals (Yes/No) with the reasons for patients who are "No" for inadequate response to topicals

- Baseline characteristics: Duration of AD disease with grouping (year; <26, ≥26 years), Pruritus numerical rating scale (NRS) for maximum or average itch intensity, Pruritus categorical scale, Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, Global Individual Signs Score (GISS), SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) Involvement of Atopic Dermatitis, Patient global assessment of disease status, Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), EQ-5D and Hospital Anxiety and Depression Scale (HADS)

4.2. Medical History and Atopic Disease Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA (18.0 at the time of BLA submission) at the coding CRO. Information on conditions related to AD includes diagnosis of AD and AD treatment history, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy hives and other allergies due to medications, animals, plants, mold, dust mites, etc. Recent AD history within 1 year before the screening visit is also collected with information of number of AD flares and episodes of skin infections requiring pharmacological treatment.

4.3. Pre-treatment/ Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the EOS visit.

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

Prohibited concomitant medications/procedures during the study

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

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with TCS or TCI

- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

Rescue treatments for AD: If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator.

Patients who receive rescue treatment during the study treatment period will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment.

If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) study treatment will be immediately discontinued.

After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

All patients will complete the schedule of 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 labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure. A predetermined algorithm for rescue medications listed in Appendix 10.6 will be used to programmatically search the concomitant medications (CMs). The rescue CMs will review and adjudicate by the medical monitor in a blinded fashion. Similarly, the rescue procedures will also be manually adjudicated by the medical monitor from the concomitant procedure data.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variable

During discussions with health authorities, different health authorities requested different primary endpoints, although the conduct of the study will be the same for all countries. As a result, the primary endpoint for US and US reference market countries is:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

For the European Union (EU) and EU reference market countries, as well as Japan, the co-primary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument to rate AD disease severity globally in clinical studies. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration. IGA score will be assessed at every scheduled and unscheduled clinic visit.

Eczema Area and Severity Index (EASI)

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 score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section.

The EASI will be collected at every scheduled and unscheduled clinic visit.

4.4.2. Secondary Efficacy Variables

The key secondary endpoints are:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this is not a secondary endpoint for the EMA EU and EU reference market countries, as well as Japan as it is already a co-primary endpoint)

- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 4
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 2

Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period using an IVRS. Patients will be asked the following questions:

- For average itches 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 overall (on average) during the previous 24 hours?"
- For maximum itches 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 IVRS to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

If there are multiple NRS to the same question (average or maximum itch intensity) collected on the same day, average of all the scores collected will be taken.

The baseline NRS is defined as the prorated average of the NRSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline NRS, The mean weekly NRS is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3. The baseline NRS and mean weekly NRS will be calculated for average itch intensity and peak itch intensity separately.

Other secondary efficacy endpoints are:

- Change from baseline to week 16 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to week 16
- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16

- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Percent change from baseline to week 2 in weekly average of peak daily pruritus NRS
- Change in ACQ-5 score from baseline to week 16
- Change in SNOT-22 score from baseline to week 16
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16. The skin infection TEAEs will be identified based on blinded adjudication of all reported TEAEs under these two primary system organ classes (SOCs): SOC = "infection and infestations" or SOC = "Skin and subcutaneous tissue disorders". Blinded adjudication will be done and finalized by the study medical monitor before database lock.
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16

Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body (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 every scheduled and unscheduled clinic visit.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993). The extent of AD is assessed by the Investigator as a percentage of each defined body area 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 (erythema, oedema / papulation, excoriations, lichenification, oozing / crusts and dryness) of AD is assessed by the Investigator 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 (VAS), 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. The maximum SCORAD score is 103.

Patients will undergo this assessment at every scheduled and unscheduled clinic visit.

Global Individual Signs Score (GISS)

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally by the Investigator (i.e., each assessed for the whole body, not by anatomical region) on a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe) using the EASI severity grading criteria. The cumulative score is the sum of the four components, which will be ranged from 0 to 12. The GISS will be assessed at every scheduled and unscheduled clinic visit.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire (Badia 1999) used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on Quality of Life (QoL). The format is a simple response to 10 items, which assess QoL over the past week. For each item, the scale is rated as follows: 0='not at all'='not relevant'; 1='a little'; 2='a lot'; 3='very much'='yes' in question 7, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. For general inflammatory skin conditions a change in DLQI score of at least 4 points is considered clinically important (Basra 2015).The DLQI will be assessed at every scheduled and unscheduled clinic visit.

Handling missing items from DLQI:

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.

ii. If two or more questions are left unanswered the questionnaire is not scored.

iii. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.

iv. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.

v. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

vi. The DLQI can be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6

Treatment	Question 10	Score maximum 3

Hospital Anxiety and Depression Scale (HADS)

The HADS is a Likert-scale tool widely used to detect states of anxiety and depression in a general hospital setting (Bjelland 2002). The 14 items on the questionnaire, assessing how the patient has been feeling in the past week, include 7 items that are related to anxiety (odd numbered questions) and 7 items that are related to depression (even numbered questions). Questions 2, 4, 7, 9, 12, and 14 are scored from 0 (less distress) to 3 (greater distress) according to the content of the item. Questions 1, 3, 5, 6, 8, 10, 11, and 13 are reverse scored from 0 (greater distress) to 3 (less distress). A person can score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8–10 represents 'probable case' and 0–7 'not a case' (Zigmond 1983).

For each sub-scale: if one question is missing, the response will be imputed as the mean of the remaining six questions. If more than one question is missing, then the subscale is set to missing. The total score is the sum of the two sub-scores.

HADS will be assessed at every scheduled and unscheduled clinic visit.

Patient Oriented Eczema Measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with atopic eczema (Charman 2004). The format is patient response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week and each item is a 5-point scale (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4 days', 3 = '5 to 6' days, and 4 = 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28 and reflects disease-related morbidity; a high score is indicative of a poor QOL.

The following POEM banding scores have been established (Charman 2004): 0 to 2 = Clear or almost clear; 3 to 7 = Mild eczema; 8 to 16 = Moderate eczema; 17 to 24 = Severe eczema; 25 to 28 = Very severe eczema. If two or more response options are selected for a question, then the response option with the highest score is recorded. If one question of the seven is left unanswered, then that question is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28.

If two or more questions are left unanswered, then the questionnaire is not scored and is set to missing.

The POEM will be assessed at every scheduled and unscheduled clinic visit.

DLQI, HADS and POEM will be administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

4.4.3. Other Efficacy Variables

Other efficacy variables include:

- Change and percent change from baseline to week 16 in EQ-5D

- Proportion of patients who respond "absence of pruritus" or "mild pruritus" in PCS at week 16
- Proportion of patients who respond "very good" or "excellent in Patient Global Assessment of Disease Status at week 16
- Proportion of patients who respond "very good" or "excellent in Patient Global Assessment of Treatment Effect at week 16
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to week 16
- Proportion of patients who achieve reduction of IGA score by ≥3 from baseline to week 16
- Sick Leave/Missed School Days Assessment

Pruritus Categorical Scale (PCS)

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in clinical studies of AD and has less of a "middling" effect (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 IVRS to complete the pruritus categorical scale at the screening visit. Patients will complete the categorical scale daily through week 16, and weekly thereafter through the last study visit. Clinical sites will receive alerts when patients do not complete IVRS items. Sites will be expected to contact patients who have missed 2 consecutive IVRS entries to encourage patient compliance.

For each day, if there are multiple PCS scores collected on the same day, the maximum (worst) of all the scores collected will be chosen. For each week, calculate round prorated average of collected scores for Category Score. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3 round to 1.0.

The baseline PCS is defined as the round prorated average of the PCSs reported continuously for 7 days right before the baseline visit.

Patient Global Assessment of Disease Status

Patients will rate their overall wellbeing based on a 5-point Likert scale. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing". Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5). Patients will undergo this assessment at the following visits: screening, day 1/baseline (pre-dose), and days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

Patient Global Assessment of Treatment Effect

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4);

"Excellent" (5). Patients will undergo this assessment at the following visits: days 15, 29, 43, 57, 85, 113, 141, 169 and 197 (EOS) or ET, and any unscheduled visits.

EQ-5D

The EuroQoL 5-Dimension Health Questionnaire 3 Level (EQ-5D-3L) is a standardized measure of health status developed by the EuroQoL group in order to provide a simple, generic measure of health for clinical and economic appraisal (Greiner 2005). The EQ-5D-3L is a self-administered questionnaire used to assess health status 'today' that is divided into two sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3).

A composite health index is then defined by combining the levels for each of the 5 dimensions, potentially producing 243 different states. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health." Values for the 243 theoretically possible health states defined by the EuroQoL classification are calculated using a regression model and weighted according to the social preferences of the UK population. The minimum value for the single index utility score is –0.594.

The second section of the questionnaire, the EuroQoL Visual Analogue Scale (EQVAS), measures self-rated (global) health status in terms of a visual analogue scale where 100 represents the best possible health state and 0 represents the worst possible health state. EQ-5D-3L self-reported VAS data generates information on the self-perceived overall health-related quality of life. Appendix 10.4 provides the SAS code to derive the index utility score using UK based population.

EQ-5D-3L will be assessed at every scheduled and unscheduled clinic visit and administered only to a subset of patients who fluently speak a language in which the questionnaire has been translated.

Juniper Asthma Control Questionnaire (ACQ-5)

The 5-question (symptoms only) version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of asthma and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6 = maximum impairment). A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ, any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing value, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

Sinonasal Outcome Test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on QOL. The questionnaire will be administered only to the subset of patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at screening and day 1/baseline, and days 113, 197 (EOS) and ET.

It contains 22 items. The total score of the SNOT-22 is calculated by summation of all the item scores. The total score ranges from 0 to 110. The MCID is equal to 8.9. For patients where some SNOT-22 items were incomplete, a total score for the SNOT-22 will be imputed as mean of the completed items, providing at least 50% of items have been completed. If more than 50% of items are missing, the total score will be considered as missing.

Twenty two items are classified into five domains as in following table. The score for each domain is the sum of response to each question in that domain. Domain score will be imputed as mean of the completed items in that domain, providing at least 50% of items in that domain have been completed.

Domain	Items
Nasal	2, 3, 4, 6, 7, 12
Ear	8, 9, 10
Sleep	13, 14, 15, 16
General and practical	1, 5, 11, 17, 18, 19
Emotional	20, 21, 22

Assess Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at day 1/baseline, days 29, 57, 85, 113, 141, 169, 197 (EOS), unscheduled visits and ET.

4.5. Safety Variables

4.5.1. Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term", "High Level Term" and the associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0 at the time of BLA submission).

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal (investigational) product.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

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

The pre-treatment period is defined as the period from the subject providing informed consent up to the first dose of study drug. The treatment and follow-up period is defined as the period from the administration of first study dose to the EOS visit.

The pre-treatment AE and treatment emergent AE (TEAE) is defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during pre-treatment period.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered as TEAEs.

4.5.2. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Blood samples for serum chemistry and hematology testing will be collected at screening (day -35 to day -1), baseline (day 1), on days 29, 57, 85, 113, 197 (EOS) or ET, and at unscheduled visits. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population.

Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory.

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[1]

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be reflexly measured when CPK >5X the ULN

Hematology with Differential

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

Urinalysis

Urine samples for urinalysis will be collected to measure overall patient health at screening, and will also be collected at (day -28 to day -1), baseline (day 1), on days 113, 197 (EOS) or ET, and at unscheduled visits.

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

4.5.3. Vital Sign Variables

The following vital signs parameters will be collected:

- Weight (kg) and height (cm)
- Respiratory rate (bpm)
- Heart rate (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)

- Body temperature (°C)

Weight is determined at screening and day 1/baseline, and days 113, 197 (EOS), any unscheduled visit, or ET. Height is only measure at screening. Other vital signs are collected pre-dose at every scheduled and unscheduled clinic visit. In addition, blood pressure and heart rate will be taken at 30 minutes (± 10 minutes) post-injection at visits 2 (day 1), 3 (week 1), and 4 (week 2) during the in-clinic 30-minutes post-injection observation. If there are multiple measurements within the time window, the last value will be included.

4.5.4. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] =QT/[$RR^{0.33}$] and QTc Bazett [QTcB]=QT/[$RR^{0.5}$]) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at screening, days 113 and 197 (EOS) or ET.

4.5.5. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.

A thorough and complete physical examination will be performed at screening, day 113, and day 197 (EOS) or ET.

4.6. Pharmacokinetic (PK) Variables

This section provides the outline of the PK variables for the study and details of PK variables will be describe separately in PK analysis plans

- Characterization of functional dupilumab concentrations in through week 16
- Correlation analyses:
  - Body weight vs functional dupilumab concentrations
  - Functional dupilumab concentrations vs clinical outcomes

Samples for drug concentration will be collected at day 1/baseline (pre-dose), days 15, 29, 57, 85, 113, 197 (EOS), unscheduled visits and ET. Pharmacokinetic variables may include but not limited to C_{trough} over time, $C_{last,}$ $T_{last,}$ time to steady state and $C_{troughSS}$ (steady state trough concentration).

4.7. Antibody (ADA) Variable

The variables include ADA status (positive or negative) and titer as follows:

- Total subjects negative in the ADA assay at all time points analyzed
- Total subjects positive in the ADA assay at any time point analyzed
- Total subjects with preexisting immunoreactivity
- Pre-existing immunoreactivity- defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response

at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels.

- Total subjects with treatment emergent response is 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 as Persistent, Indeterminate or Transient
  - Persistent Response - Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 85 days), with no ADA negative samples or any missing sample in between.
  - Indeterminate Response - as a treatment-emergent response with only the last collected sample positive in the ADA assay
  - Transient Response - a treatment emergent ADA positive assay response that is not considered persistent or indeterminate.
- Total subjects with treatment boosted response
- 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 Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

ADA positive samples will be further characterized for the strength of the ADA response by assessment of ADA titers and for the presence of neutralizing antibody (NAb) response.

4.8. Biomarkers

Biomarkers to be analyzed in this study are:

- TARC and total serum IgE
- antigen-specific IgE
- hs-CRP, ANA, anti dsDNA, anti-TPO

TARC and total serum IgE are markers of Th2 activity and are downstream of IL-4/13 signaling. These analytes will be assessed as measures of Th2 activity and pharmacodynamic effect of the drug.

Patients with total serum IgE levels in the normal range may still have antigen-specific IgEs in circulation, indicating they are atopic. To further understand atopy in this patient population, region-specific, allergen-specific IgE panels will be performed.

The role that Th2 immune function plays in regulating other immune functions is not well understood. To investigate whether or not dupilumab suppression of Th2 activity results in an increase in non-Th2-mediated inflammation or autoimmunity, hs-CRP and autoantibodies (anti-dsDNA, anti-TPO, and ANA) will be measured.

Samples will be collected at time points according to the schedule in Appendix 10.2.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

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

5.1. Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups based on FAS. Listing of demographics and baseline characteristics will be presented.

5.2. Medical and AD History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

Medical history will be listed, sorted by treatment groups based on the SAF.

5.3. Pre-treatment/Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications, prohibited medications/procedures and rescue medications/procedures will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined dupilumab treatment groups.

The procedure will be summarized by treatment group to MedDRA 18.0 at the time of BLA submission by system organ class (SOC) and preferred term (PT) and sorted by decreasing frequency of SOC and PT, based on the overall incidence for combined dupilumab treatment groups.

Listing of pre-treatment medication and concomitant medications will include generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, route.

The detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized by topical and systemic groups. Kaplan Meier curves for time to first rescue use will be generated.

The compliance of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group.

5.4. Subject Disposition

The following summaries by table will be provided:

- The total number of screened patients
- 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 treatment and the reasons for the discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation
- Number of patients who entered into follow-up period

The following listings will be provided:

- Listing of subject disposition including: date of randomization, date of the last visit, received dose, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized, including the patients who missed active study drug doses to the point that their cumulative exposure ends up being closer to another study regimen that is different from the one to which they had been randomized (e.g., a patient randomized to 300 mg qw who missed 30-50% of doses will be closer to 300 mg q2w than to the originally assigned 300 mg qw)
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation, summary tables of reasons will be provided
- Summary table with listing of protocol deviations will be provided

5.5. Dose Administration

The compliance with protocol-defined investigational product will be calculated as follows:

Treatment Compliance= (Number of injections during exposure period) / (Number of planned injections during exposure period) x 100%

Loading doses for the same patient will be counted as 1.

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80% and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information and whether or not the total dose is administered for each dose will be presented.

If subjects received treatment different from the randomized treatment or stopped treatment due to an AE, or overdosed, the listings will be provided.

5.6. Treatment Exposure and Observation Period

The duration of treatment exposure period during the study is calculated as:

(Date of last study drug injection – date of first study drug injection) + 7

Note: exposure will be calculated based on the last study drug injection date and first study drug injection date regardless of temporary dosing interruption.

The duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well:

≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days, ≥98 days, ≥112 days, ≥126 days, ≥140 days, ≥154 days, ≥ 168 days, ≥182 days, ≥196 days.

The duration of observation period during the study is calculated as:

[Date of the last study visit – date of the first study injection] +1.

The duration of observation period will be summarized descriptively as a quantitative data (n, mean, SD, median, minimum and maximum). In addition, The number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest is specified as:

≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 43 days, ≥50 days, ≥ 57 days, ≥ 64 days, ≥ 71 days, ≥ 78 days, ≥ 85 days, ≥99 days, ≥113 days, ≥127 days, ≥141 days, ≥155 days, ≥169 days, ≥183 days, ≥197 days.

5.7. Analyses of Efficacy Variables

For all efficacy variables, the analysis will be comparisons of each dupilumab regimen and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested for each dupilumab regimen group and the placebo group:

H0: $p_{dupilumab} = p_{placebo}$, where p stands for the proportion of responders in a treatment group

H1: $p_{dupilumab} \neq p_{placebo}$.

The analyses of efficacy variables are described in the subsections below and summarized in Appendix 10.1.

Subgroups are defined by key baseline factors recorded on the CRF and listed to be considered for primary and secondary efficacy analyses:

- Age group (≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black, Asian, Other)
- Duration of AD (< 26 years, ≥26 years)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)
- BMI (<15, ≥15-<25, ≥25-<30, ≥30
- Region for global submission (Asia Pacific, Eastern Europe, North and South America, Western Europe)
- Baseline disease severity [moderate (IGA=3) and severe (IGA=4)]
- Baseline moderated-to-severe EASI (<20, ≥20)
- Baseline severe EASI (<25, ≥25)
- Baseline peak NRS (<7, ≥7)
- Baseline Body Surface Area (BSA) (≥10%-<30%, ≥30%-<50%, ≥50%)
- Baseline SCORAD score (≤ 50, >50)
- Previous use of systemic immunosuppressants for AD (Yes, No)
- Previous use of systemic cyclosporine for AD (Yes, No)
- Previous usage of Azathioprine (Aza) (Yes, No)
- Previous usage of Methotrexate (MTX) (Yes, No)
- History of asthma (Yes, No)
- History of nasal polys (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergies (Yes, No)

5.7.1. Analysis of Primary Efficacy Variables

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

Handling of dropouts or adjudicated rescue medication or missing value for the binary response variables as the primary analysis

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

To account for the impact of rescue medication on the efficacy effect:

For the binary efficacy endpoints, if rescue medication is used (see Section 4.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.

If the patient has the missing value at week 16, then it will be counted as a non-responder at week 16.

Sensitivity analyses

1. Post-baseline Last Observation Carried Forward (LOCF) approach after censoring for rescue medication use or study withdrawal 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.
2. All observed data, no matter if rescue medication is used or data is collected after study withdrawal, will be included for the primary endpoint. Patients with missing value will be counted as non-responder.
3. All observed data, no matter if rescue treatment is used or data is collected after study withdrawal, will be included for the primary endpoint (regardless of rescue medication used), missing data will not be imputed as non-responder.

The primary efficacy analyses will be performed on FAS, as well as on PPS as a supporting analysis.

5.7.2. Analyses of Secondary Efficacy Variables

The binary secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoints.

The endpoint "Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16" will only be analyzed for patients with baseline peak pruritus NRS ≥4.

The continuous endpoints will be analyzed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model as the primary analysis for continuous variables. Patients' efficacy data through week 16 after the rescue medication usage will be set to missing first, and then be imputed by the multiple imputation method. Missing data from the FAS will be imputed 50 times to generate 50 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. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, randomization strata (region, disease severity), and relevant baseline.

The week 16 data of each of the 50 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata (region, disease severity), 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 50 analyses using Rubin's formula.

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, the baseline value and the randomization strata
- Measured endpoint values from every clinic visit up to week 16

Categorical variables included in above model (i.e., treatment group and randomization strata) are not expected to be missing.

To account for the impact of rescue medication on the efficacy effect:

- Continuous efficacy endpoints: if a patient receives rescue medication that specifies the patient as a non-responder according to the above rules for binary efficacy endpoints, the data collected after rescue medication is initiated will be treated as missing.

Sensitivity analyses

In addition to the MI method described previously, sensitivity analyses for the continuous endpoints for EASI and/or Pruritus NRS will be conducted as described below:

1. The sensitivity analysis based on all observed data no matter if rescue medication is used or data is collected after withdrawal using MI method will be performed.
2. This sensitivity analysis will use a mixed-effect model repeated measures (MMRM). The model will include factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within-patient errors. Denominator degrees of freedom will be estimated using approximation of SATTERTH. The efficacy data will be set to missing after rescue medication is used. Afterwards no imputation will be made.

   The MMRM model will provide least-squares means at week 16 and at other time points for each treatment group with the corresponding standard error, confidence interval, and the p-value for treatment comparisons. The graph of LS-mean +/- se by visit will be provided.
3. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue medication is used. The post-baseline LOCF method will then be used to impute missing values.
4. This sensitivity analysis will use ANCOVA model, including the treatment group, the baseline value and the randomization strata. The efficacy data will be set to missing after rescue medication is used. The post-baseline worst-observed-case-forward (WOCF) method will then be used to impute missing values.
5. This sensitivity analysis will use ANCOVA model, including study, the treatment group, the baseline value and the randomization strata. The efficacy data will be based on all

observed value regardless rescue medication used. No imputation method will be applied for the sensitivity analysis.

Analysis of incidence of TEAE-related variables

- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16

These endpoints will be analyzed for patient in SAF. The week 16 treatment period is defined in Section 3.3. The Cochran-Mantel-Haenszel test adjusted for randomization strata (region, disease severity) will be used for the percentage of patients with events described above through week 16.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and placebo will be derived by testing each active dose group versus placebo separately. Two-sided 95% confidence intervals of the rate ratio will be provided. The estimated events rate and its 2-sided confidence intervals will be provided for each treatment group.

Multiplicity Considerations

For US and US reference market countries:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall type-1 error rate at 0.05 for the primary and secondary endpoints across the 2 dose regimens. For each test within each dose regimen, if the primary endpoint is significant at the 0.025 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.025 significance level of the previous one.

For EU and EU reference market countries, as well as Japan:

The following multiplicity adjustment approach, a serial gatekeeping procedure, will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. For each dose regimen, an intersection-union method will be applied to the co-primary endpoints, which requires statistical significance of both co-primary endpoints at the 2-sided 0.025 level. If both co-primary endpoints are significant, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about secondary endpoints require statistical significance at the 0.025 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 16

- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 4
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to week 2
- Change from baseline to week 16 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to week 16
- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in HADS
- Percent change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Percent change from baseline to week 2 in weekly average of peak daily pruritus NRS
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 16
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16

The analysis for the above safety endpoints will be performed regardless of whether any endpoint before these in the hierarchy is significant or not.

5.7.3. Analyses of Other Efficacy Variables

Analyses of categorical variables will be similar to the primary analysis; analyses of continuous variables similar to the secondary analyses.

Changes from baseline to each measurement visit in ACQ-5 and SNOT-22 will be summarized by treatment group and visit. Number of sick Leave/missed school days from each assessment will be summarized by treatment group.

5.8. Analysis of Safety Data

The summary of safety and tolerance will be performed based on SAF.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs, and 12-lead ECG.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables, vital signs and ECG are defined in Appendix 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

Subgroups are defined by key baseline factors recorded on the CRF and listed to be considered for safety analyses:

- Age group (≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black, Asian, Other)
- Duration of AD (< 26 years, ≥26 years)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)

5.8.1. Analysis of Adverse Events

The number and proportion of patients will be summarized separately for the week 16 treatment period, the follow-up period and overall study period, described in Section 3.3. Adverse event (AE) incidence tables will be presented for each treatment group along with total of dupilumab doses as well as for selected subgroups, including the number (n) and percentage (%) of patients experiencing an AE, where multiple instances of the same event occur in the same patient the event will be counted only once for that patient, at the first dose level in which it occurs (when applicable). The denominator for computation of percentages is the number of patients in each treatment group, across all dupilumab regimens.

The number and proportion of patients reporting TEAEs will be summarized, sorted by decreasing frequency of SOC and PT for the highest dupilumab dose. The number and proportions of patients reporting TEAEs will also be summarized, sorted by decreasing frequency of SOC, HLT and PT for the highest dupilumab dose.

Patient listings will be provided for all SAEs, death, and TEAEs leading to permanent treatment discontinuation.

The following variables will be included in the listing:

- Patient ID
- Treatment group

- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)
- Verbatim Term
- AE start date and end date/ongoing (using both calendar days and study days)
- AE Duration
- Relationship of AE to study drug: unrelated or related
- Action taken: Dose withdrawn temporarily, Dose reduced, Dose withdrawn permanently, Dose not changed, Not known or Not applicable
- Severity: using a 3–point scale (mild, moderate, or severe)
- Treatment: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with sequelae, recovering/ resolving, not recovered/not resolved, fatal or unknown

In addition, to account for potentially differential exposure time, two types of exposure-adjusted analyses will be provided, namely, Number of Events per 100 Patient-Year (NEPY) and Number of patients with at least one event per 100 patient-years. These calculations will be adjusted for dose exposure for the Week 16 treatment period and for the entire study period.

Number of events per 100 patient-years (NEPY)

The NEPY will be calculated as the number of events occurring in the population divided by the sum of the exposure over all patients (i.e., total exposure) in the TEAE period.

$$NEPY = 100 \times \frac{\sum n_i}{\sum T_i}$$

where n_i is the number of events observed for patient i; T_i is total TEAE exposure for patient i in person-year unit.

Number of patients with at least one event per 100 patient-years

The exposure-adjusted incidence rate (EAIR) can be defined as the number of patients with at least one specific adverse event per 100 patients taking the treatment for 1 year (52 weeks). The number of patients with at least one event per 100 patient-years will be calculated as the number of patients having a specific event divided by the total person-year and at risk of an initial occurrence of the event. In particular, the EAIR is computed as follows:

$$EAIR = 100 \times \frac{n}{\sum t_i}$$

where n is the number of patients with the specific adverse event; it is a patient's exposure time in person-year unit. For each of the adverse events of interest, the exposure time t_i for patients who have experienced the adverse experience will be defined as the time to first adverse

experience, whereas the exposure time for those who have not had this adverse experience will be total duration of exposure in the TEAE period.

The time to first AESIs (TEAE by category) or TEAE leading to permanent treatment discontinuation will be assessed by Kaplan-Meier estimates (K-M plot). In order to detect any safety signals, the hazard ratio (HR) will be provided together with the corresponding 95% confidence interval (CI) for the selected adverse events during the 16 week treatment period. Hazard ratios will be calculated using a Cox model including factors of treatment group, and randomization strata. The time is defined as the date of first event – the date of first dose + 1. Patients without an event will be censored at the end of 16-week treatment period. Graphs of cumulative incidence rate over time will be presented by treatment group.

Overall TEAE summary

The overall summary of TEAEs will be provided with number and proportions of patients with any:

- TEAE
- TEAE related to study drug
- Serious TEAE
- TEAE of special interest (AESI)/TEAE by syndrome
- TEAE leading to death
- TEAE leading to permanent treatment discontinuation
- TEAEs leading to temporary treatment discontinuation by SOC and PT

AESI/TEAE by syndrome

- Anaphylactic reactions
- Acute allergic reaction
- Severe injection site reactions that last longer than 24 hours
- Mycosis fungoides
- Cutaneous T-cell dyscrasia
- Any severe infection
- Any infection requiring treatment with parenteral antibiotics
- Any infection requiring treatment with oral antibiotics/anti-viral/anti-fungal for longer than 2 weeks
- Any clinical endoparasitisis
- Any opportunistic infection
- Suicidal behavior

Appendix 10.5 provides a list of AESIs search criteria.

TEAE Incidence

Number and proportions of patients reporting TEAEs will be summarized for the following TEAEs:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - TEAEs by SOC/HLT/PT with HLT ≥5% in any treatment groups
  - TEAEs by SOC/HLT/PT with PT ≥5% in any treatment groups
  - TEAEs by SOC/PT with PT ≥5% in any treatment groups
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - Severe TEAEs by SOC/HLT/PT
  - TEAEs related to study medication as assessed by the investigator by SOC/PT
  - Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
  - TEAE of special interest/TEAE by category
- Serious TEAEs
  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLT/PT
  - Serious TEAEs related to study medication as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- TEAEs leading to temporary discontinuation of study treatment by SOC/PT
- Death by SOC/PT

Exposure-adjusted TEAE Incidence Rates (in patient-years)

The number of patients with event per 100 patient-year will be summarized in the week 16 treatment period and follow-up period and the overall period

- TEAEs by SOC and PT
- Severe TEAEs by SOC/PT
- TEAEs related to study medication as assessed by the investigator by SOC/PT
- Severe TEAEs related to study medication as assessed by the investigator by SOC/PT

- Serious TEAEs by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- TEAEs leading to temporary discontinuation of study treatment by SOC/PT

Number and proportions of subjects reporting TEAEs listed above will be summarized, sorted by decreasing frequency of SOC and PT for the highest dose level

Summaries of TEAEs will include:

- Proportion of subjects with at least one TEAEs
- Proportions of subjects with at least one TEAEs by SOC/PT
- Proportions of subjects with at least one TEAEs by SOC/HLT/PT
- Proportions of subjects with at least one TEAEs by PT
- Proportion of subjects with at least one TEAEs by severity by SOC/PT
- Proportion of subjects with at least one TEAEs related to study medication by SOC/PT
- Proportion of subjects with at least one serious TEAEs by SOC/PT
- Proportion of subjects with TEAEs leading to discontinuation of study treatment by SOC/PT

Summary of the most frequent (≥5%) TEAEs by SOC, HLT, PT, respectively, in the aggregate dupilumab groups and in the overall study population will be provided.

SAEs/AESI during the Week 16 treatment period, follow-up period and overall period will be listed.

5.8.2. Analysis of Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with abnormal lab value during study whose screening and baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs during study, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by subject and visit will be provided.

5.8.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings will be provided with flags indicating the treatment-emergent PCSVs, depending on data.

5.8.4. Analysis of Physical Exams

The number (n) and percentage (%) of subjects with abnormal physical exams will be summarized at baseline, end of treatment period and end of study by treatment group. A summary of treatment-emergent abnormal findings will be provided.

5.8.5. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings will be provided with flags indicating PCSVs, depending on data.

5.9. Analysis of Pharmacokinetic Data

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Least square mean analysis for concentration at steady-state

No formal statistical analysis will be performed.

5.10. Analysis of ADA Data

The ADA variables described in Section 4.7 will be summarized using descriptive statistics by dose cohorts in the ADA analysis set. Frequency tables of the proportion of patients developing ADA positivity in the ADA assay, Neutralizing antibody status in the NAb assay, pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent, indeterminate and transient ADA responses and titers will be presented as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Listing of all ADA peak titer levels and neutralizing antibody status will be provided for ADA positive subjects.

The following summaries will be performed on the AAS:

- Number (%) of patients ADA positive at any time at time points analyzed by treatment group
- ADA peak titers using descriptive statistics (median, minimum and maximum) by treatment group
- ADA titers using descriptive statistics (median, minimum and maximum) by treatment group and ADA collect visit indicated in Appendix 10.2.
- Number (%) of patients with NAb status (negative or positive) by treatment group
- Number (%) of patients with pre-existing ADA, treatment-emergent ADA, and treatment boosted ADA response by treatment group
- Number (%) of patients with persistent, transient and indeterminate treatment-emergent ADA response by treatment group

Correlations between ADA variables (e.g. ADA peak titers, neutralizing antibody status, treatment-emergent, treatment-boosted, transient, indeterminate and persistent ADA responses) and PK may also be explored (e.g, scatter plot) and the detailed analysis will be described separated in the PK analysis report

Impact of ADA on Safety and Efficacy

Correlation analysis of safety versus ADA positive status and neutralizing antibody status may be performed in SAF.

The safety assessment will focus on the following events:

Hypersensitivity (SMQ: Hypersensitivity [Narrow])

- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Number (%) of patients with the above mentioned safety events will be summarized by ADA status (positive or negative), and presence of neutralizing antibody (positive or negative) during the TEAE period.

In addition, the primary endpoint and key secondary efficacy endpoints will be summarized in patients with and without ADA (positive vs. negative) and neutralizing antibody (positive or negative) status if applicable.

5.11. Analysis of Biomarkers

Descriptive statistics for the observed value, change and percent change from baseline value by treatment and visit will be provided for the following biomarker variables:

- TARC (screening, days 1, 15, 29, 57, 85, 113, 197)
- total serum IgE (screening, days 1, 29, 57, 85, 113, 141, 169, 197)
- antigen-specific IgE (screening, days 1, 29, 57, 85, 113, 197)
- hs-CRP (screening, days 1, 57, 85, 113, 197)

Proportions for the following binary biomarkers will be reported:

- ANA, anti dsDNA, anti-TPO (screening, days 1, 57, 85, 113, 197)

The Wilcoxon signed-rank test stratified by the baseline disease severity will be used to test if the change or percentage change from baseline value is significantly different from zero. P-value will be reported.

Exploratory analyses for the difference between dupilumab groups and placebo on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group and the baseline disease severity as fixed effects, and the relevant baseline values as covariate. Missing value will be imputed by LOCF method for visits between post-baseline to visit 18 (week 16). After visit 18, no imputation will be made. P-value for difference from placebo will be provided.

Correlation of baseline TARC (measured value) and IgE (measured value) with the following clinical endpoints will be explored using the Spearman's rho test. Both Spearman correlation coefficients and p-value will be reported.

- Percent change from baseline to week 16 in EASI score
- Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS
- Change from baseline to week 16 in percent BSA
- Percent change from baseline to week 16 in SCORAD

Association of baseline TARC (measured value) and IgE (measured value) with the following clinical endpoints will be explored using the ANOVA model. The model will include the baseline biomarker value as the dependent variable, and the responder/non-responder from the endpoint, the baseline disease severity and the treatment group as the categorical factor. P-value will be provided to show significance of the responder/non-responder factor.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16

Association of positivity to at least one antigen-specific IgE with the following clinical endpoints will be explored using CMH test stratified by the baseline disease severity. The risk ratio and p-value from the chisq test will be provided.

- IGA 0-1 at week 16
- EASI-75 at week 16
- improvement (reduction) of weekly average of peak daily pruritus NRS ≥3 from baseline to week 16

Correlation/association will be implemented on the Placebo, dup 300 mg Q2W, dup 300 mg QW and combined dupilumab (dup 300 mg Q2W and QW) groups, respectively.

Shift tables from baselines status to post-baseline status by visit and by phases of treatment period and whole observation period until EoS will be provided for hs-CRP, ANA, anti dsDNA and anti-TPO variables will be provided by treatment group. The standard line plots (means +/- se) for continuous variables will be provided.

All above analyses will be performed on the FAS for

- All observed data, no matter if rescue medication is used or data is collected after study withdrawal
- All observed data with censoring after rescue medication use or study withdrawal.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of NRS is defined in Section 4.4.2 Secondary Efficacy Variables. The following rules specify the determination by both date/time information:

1. For the AE, lab (including biomarker), PK and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.
2. For other data except AE, lab (including biomarker), PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen- failure subject ID or enrolled subject ID.

6.2. General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAE. For example, if the assessment of relationship of a TEAE to the

investigational product is missing, it will be classified as "related" in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to align with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use the last visit study date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of last study visit date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.4. Analysis Visit Window

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG, ADA) will be summarized by the study scheduled visits described Appendix 10.2, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT/EOS visits, based on the study day:

Visit No.	visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 1	8	[2,11]
4	Week 2	15	[12,18]
5	Week 3	22	[19, 25]
6	Week 4	29	[26, 32]
7	Week 5	36	[33, 39]
8	Week 6	43	[40, 46]
9	Week7	50	[47, 53]
10	Week 8	57	[54, 60]
11	Week 9	64	[61, 67]
12	Week 10	71	[68, 74]
13	Week 11	78	[75, 81]
14	Week 12	85	[82, 88]
15	Week 13	92	[89, 95]
16	Week 14	99	[96, 102]
17	Week 15	106	[103, 109]
18	Week 16 (End of Treatment)	113	[110, 127]
19	Week 20	141	[128, 155]
20	Week 24	169	[156, 183]
21	Week 28 (End of Study)	197	>=184

* Study days are calculated from 1st day of dupilumab injection

In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) or end of study (EOS), whichever comes first if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ETV/EOT/EOS are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

For the ePRO data collected daily via IVRS, the analysis visit windows will be implemented following the procedures below:

Step 1: Derive the study day,

- If diary date ≥ 1st injection date, then diary study day=diary date – 1st injection date +1;
- Otherwise diary study day=diary date – 1st injection date

Step 2: Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc, with 7 days interval between visit windows.

7. INTERIM ANALYSIS

No interim analysis is planned.

8. SOFTWARE

All analyses will be done using SAS Version 9.2 or above.

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16;	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on OC or LOCF, and on PPS	Yes	Histogram
Secondary continuous variables	FAS	MI	MMRM, ANCOVA with LOCF and WOCF	Yes for EASI and NRS endpoints	Line plot
Categorical variables	FAS	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test / LOCF	Yes for EASI and NRS endpoints	Histogram

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Events

Screening, Baseline, and Treatment Period

Study Procedure	Screening	Baseline	Treatment Period											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)	**-35 to -1**	**D1**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)			**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:														
Informed Consent	X													
ICF for optional assessments[2]	X													
Inclusion/Exclusion	X	X												
Medical History/ Demographics	X													
Randomization		X												
Training on IVRS[3]	X													
Treatment:														
Injection training/observation		X	X	X		X		X		X				X
Administer Study Drug		X[4]	X[4]	X[4]	X[1]	X	X[1]	X	X[1]	X	X[1]	X[1]	X[1]	X
Patient Dosing Diary[5]				X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation/account[6]				X		X		X		X				X
Con meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7,8]														
Pruritus NRS (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]	X	X	X	X		X		X		X				X
Patient Global Assess of Disease	X	X		X		X		X		X				X
Patient Global Assess of Treatment				X		X		X		X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X
ACQ-5, SNOT-22[9]	X	X												
Assess sick-leave/missed school days		X				X				X				X
Photograph AD area (select sites)[10]		X												

Study Procedure	Screening	Baseline	Treatment Period											
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**[1]	**V6**	**V7**[1]	**V8**	**V9**[1]	**V10**	**V11**[1]	**V12**[1]	**V13**[1]	**V14**
Week (W)	**-35 to -1**	**D1**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**
Day (D)			**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Safety:[7]														
Weight	X	X												
Height	X													
Vital Signs	X	X	X	X		X		X		X				X
Physical Examination	X													
Electrocardiogram	X													
Adverse Events	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X
Laboratory Testing:[7]														
HIV Ab, HBsAg, HBcAb, Hep C Ab, TB[11]	X													
Hematology, Chemistry	X	X				X				X				X
Urinalysis	X	X												
Pregnancy Test (WOCBP only)	Serum	Urine				Urine				Urine				Urine
TARC	X	X		X		X				X				X
Total serum IgE	X	X				X				X				X
Antigen-specific IgE sample[12]	X	X				X				X				X
hs-CRP, ANA, anti-dsDNA, antiTPO	X	X								X				
Skin microbiome samples (select sites)[13]	X	X				X				X				X
Research samples(serum/plasma)	X	X		X		X				X				X
Optional DNA sample, RNA sample		X												
PK/Drug Concentration and ADA Samples:[7]														
Functional dupilumab PK sample		X		X		X				X				X
Anti-dupilumab antibody sample		X		X		X				X				

1 The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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.

2 For patients who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA and RNA sample collection). DNA sample should be collected at the day 1 visit, but can be collected at any visit during the study. RNA sample must be collected before the administration of the first dose of study drug.

3 Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

[4] Patients will be monitored at the study site at visits 2, 3, and 4 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure and heart rate) and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[5] For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[6] Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

[7] To be collected before the injection of study drug. ADA samples collected at day 1 (baseline) at Week 16 (EOT), at Week 28 (EOS), and at early termination (ET) will be analyzed for ADA

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

[9] 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

[10] Select sites only - photograph AD area

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

[12] Includes: antigen-specific IgE (region-specific allergen panels).

[13] Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites.

Treatment Period cont., Follow-up Period, End of Study, Unscheduled Visits, and Early Termination

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Treatment:									
Injection/training/observation									
Administer Study Drug	X[3]	X[3]	X[3]						
Patient Dosing Diary[4]	X	X	X	X					X
Study drug dispensation/account[5]				X					X
Con meds/Procedures	X	X	X	X	X	X	X	X	X
Efficacy:[6,7]									
Pruritus NRS (daily)[8]	X	X	X	X	X	X	X	X	X
Pruritus Categorical Scale (daily)[8]	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[9]				X	X	X	X	X	X
Patient Global Assess of Disease				X	X	X	X	X	X
Patient Global Assess of Treatment				X	X	X	X	X	X
IGA, EASI, GISS, SCORAD, BSA				X	X	X	X	X	X
ACQ-5, SNOT-22[9]				X			X		X
Assess sick-leave/Missed school days				X	X	X	X	X	X
Photograph AD area (select sites)[10]				X			X	X	X
Safety:[6]									
Weight				X			X	X	X
Vital Signs				X	X	X	X	X	X
Physical Examination				X			X		X
Electrocardiogram				X			X		X
Adverse Events	X[8]	X[8]	X[8]	X	X	X	X	X	X
Laboratory Testing:[6]									
Hematology, Chemistry				X			X	X	X
Urinalysis				X			X	X	X
Pregnancy Test (WOCBP only)				Serum			Serum	Urine	Serum
TARC				X	X	X	X	X	X
Total serum IgE				X	X	X	X	X	X

Study Procedure	**Treatment Period**[1]				**Follow-up Period**		**EOS**[1]	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V15**[3]	**V16**[3]	**V17**[3]	**V18**	**V19**	**V20**	**V21**		
Week (W)	**W 13**	**W 14**	**W 15**	**W 16**	**W 20**	**W 24**	**W 28**		
Day (D)	**D92**	**D99**	**D106**	**D113**	**D141**	**D169**	**D197**		
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Antigen-specific IgE samples[11]				X			X	X	X
hs-CRP, ANA, anti-dsDNA, antiTPO				X			X	X	X
Skin microbiome samples (select sites)[12]				X			X	X	X
Research samples(serum/plasma)				X			X	X	X
PK/Drug Concentration and ADA Samples:[7]									
Functional dupilumab PK sample				X			X	X	X
Anti-dupilumab antibody sample[13]				X			X	X	X

1 The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

2 During an unscheduled visit, any of the study procedures noted may be performed, but not all are required

3 The site will contact the patient by telephone to conduct these visits. The patient/caregiver may administer study drug on these days. 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

4 For patients who choose to self-administer study drug during some weeks, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

5 Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

6 To be collected before the injection of study drug.

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

8 Patients will be trained at the screening visit on using the appropriate diary system to report pruritus and provide other information as required.

9 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). ACQ-5 will be administered only to patients with a medical history of asthma. SNOT-22 will be administered only to patients with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). All questionnaires will be administered before any invasive procedures (blood draws, study drug injection, etc.).

10 Select sites only - photograph AD area

11 Includes: antigen-specific IgE (region-specific allergen panels).

12 Non-invasive skin swabs; this is a sub-study that may be conducted at selected sites

13 ADA samples collected at day 1 (baseline) at Week 16 (EOT), at Week 28 (EOS), and at early termination (ET) will be analyzed for ADA

10.3. Criteria for Treatment-Emergent Potentially Clinical Significant Value (PCSV) for Dupilumab AD Studies

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and >20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and >20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided

Parameter	Treatment Emergent PCSV	Comments
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.

Parameter	Treatment Emergent PCSV	Comments
Glucose		
Hypoglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black);	Increase in WBC: not relevant.
	<2.0 Giga/L and >=2.0 Giga/L at baseline (Black)	
	≥16.0 Giga/L and < 16 Giga/L at baseline	To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black);	International Consensus meeting on drug-induced blood cytopenias, 1991.
	<1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female.	Three criteria are independent.
	≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
	Decrease from Baseline ≥20 g/L	
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline forFemale	Two Criteria are independent
	≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	

Parameter	Treatment Emergent PCSV	Comments
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	

Parameter	Treatment Emergent PCSV	Comments
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. 5 independent criteria

10.4. SAS Code for EQ-5D Index Utility Scoring

```
/*=================================================================*/;
/*  Aim                       : Derive the EQ5-D index (utility)
*/;
/*  Source for the algorithm : scoring EQ-5D health states (Rosalind Rabin
*/;
/*            (cf. G:\_HE\PRO questionnaire\EQ5D\scoring\YorkTariffx.doc)
*/;
/*  Note                      : UK based population (Dolan, 1997)
*/;
/*  Author                    : Elisheva Smadja
*/;
/*=================================================================*/;

data EUROQOL;   set temp;
   profil= (10000*eqq1cd)+(1000*eqq2cd)+(100*eqq3cd)+(10*eqq4cd)+eqq5cd;
   eq5d=1;
**********Mobility*********;
if eqq1cd=2     then eq5d=eq5d-0.069;
if eqq1cd=3     then eq5d=eq5d-0.314;
********Self-care**********;
if eqq2cd=2     then eq5d=eq5d-0.104;
if eqq2cd=3     then eq5d=eq5d-0.214;
******Usual activities*****;
if eqq3cd=2     then eq5d=eq5d-0.036;
if eqq3cd=3     then eq5d=eq5d-0.094;
*****Pain/discomfort******;
if eqq4cd=2     then eq5d=eq5d-0.123;
if eqq4cd=3     then eq5d=eq5d-0.386;
*****Anxiety/depression*****;
if eqq5cd=2     then eq5d=eq5d-0.071;
if eqq5cd=3     then eq5d=eq5d-0.236;

if (eqq1cd ne 1 or eqq2cd ne 1 or eqq3cd ne 1 or eqq4cd ne 1 or eqq5cd ne 1)
                then eq5d=eq5d-0.081;
if (eqq1cd=3 or eqq2cd=3 or eqq3cd=3 or eqq4cd=3 or eqq5cd=3)
                then eq5d=eq5d-0.269;
if (eqq1cd=. or eqq2cd=. or eqq3cd=. or eqq4cd=. or eqq5cd=.)
                then eq5d=.;
run;
```

10.5. Search Criteria for TEAE of Special Interest/TEAE Syndrome

AESI	Search Criteria
Anaphylactic reactions	Narrow SMQ for "anaphylactic reaction"
Acute allergic reactions that require treatment	• Narrow SMQ for "hypersensitivity" • TEAE occurred due to the medication taken and recoded on ConMed CRF page *Note: Blinded manual adjudication of relevant PTs will be required by the study medical monitor, before database locks*
Severe ISRs that last longer than 24 hours	-HLT = Injection site reactions - Severity = "severe"
Mycosis fungoides or other forms of cutaneous T cell lymphoma	-HLT = "Mycosis fungoides" • Includes LLT = Sezary syndrome • Includes LLT = Cutaneous T-cell lymphoma -PT = "Cutaneous T-cell dyscrasia
Any severe infection	-SOC = Infections and infestations -Severity = "severe
Any infection requiring treatment with parenteral antibiotics	-SOC = Infection and infestations -Action taken for AE = "medication" - ConMed: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = IV, IM
Any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks	-SOC = Infection and infestations -Action taken for AE = "medication" -Check CM: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = PO and Treatment duration >14 days
Any clinical endoparasitosis	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection
Any opportunistic infection[a]	The following HLTs plus PTs -HLT = Pneumocystis infection -HLT* = Fungal infections NEC -HLT* = Pseudallescheria infections -HLT = Herpes viral infections -HLT = Paracoccidioides infections -HLT = Sporothrix infections

AESI	Search Criteria
	-HLT = Cryptosporidia infections -HLT* = Trypanosomal infections -HLT* = Campylobacter infections -HLT* = Shigella infections -HLT* = Vibrio infections Plus the following PTs -Polyomavirus-associated nephropathy -BK virus infection -Cytomegalovirus infection -Post transplant lymphoproliferative disorder -Progressive multifocal leukoencephalopathy -*Bartonellosis -Blastomycosis -Toxoplasmosis -Coccidioidomycosis -Histoplasmosis -*Aspergillus infection -Systemic candida -Oropharyngeal candidiasis -Cryptococcosis -Listeriosis -Tuberculosis -Nocardiosis -Mycobacterial infection -*Salmonellosis -*Hepatitis B -Herpes zoster -*Strongyloidiasis -Microsporidia infection -Visceral leishmaniasis -*Hepatitis C *Note: *Blinded manual adjudication of relevant PTs under each of HLTs listed above will be required by the study medical monitor, before database locks*
Suicidal behavior	Include the following PTs -Completed suicide -Suicidal ideation -Suicidal behavior -Depression suicidal -Suicide attempt

[a] The definition of opportunistic infections is referring to the recent consensus guidance for opportunistic infections in the setting of biologic therapy

10.6. Algorithm for RESCUE TREATMENTS

1. Not required to adjudicate rescue treatment:
   Post-baseline medications (WHODD-coded) given for indications consistent with AD [1]
   a. Always considered rescue:
      - ATC2 = CORTICOSTEROIDS FOR SYSTEMIC USE
      - ATC2 = IMMUNOSUPPRESSANTS
      - Preferred Drug Name = Ciclosporin
      - Preferred Drug Name = Methotrexate
      - Preferred Drug Name = Mycophenolate sodium
      - Preferred Drug Name = Mycophenolic acid
      - Preferred Drug Name = Mycophenolate mofetil
      - Preferred Drug Name = Azathioprine
      - ATC2 = CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, if used on or after Day 15
      - Preferred Drug Name = Tacrolimus, if used on or after Day 15
      - Preferred Drug Name = Pimecrolimus, if used on or after Day 15
   b. Never considered rescue
      - ATC2 = EMOLLIENTS AND PROTECTIVES
      - ATC2 = VASOPROTECTIVES
      - ATC2 = ANALGESICS
      - ATC2 = ANTI-ACNE PREPARATIONS
      - ATC2 = TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
      - ATC2 = ANTIBACTERIALS FOR SYSTEMIC USE
      - ATC2 = ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
      - ATC2 = ANTIVIRALS FOR SYSTEMIC USE
      - ATC2 = ANTIFUNGALS FOR DERMATOLOGICAL USE
      - ATC2 = ANTISEPTICS AND DISINFECTANTS
      - ATC2 = ANTIHISTAMINES FOR SYSTEMIC USE
      - ATC2 = ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.
      - ATC2 = ANTIPSORIATICS (except Preferred Drug Name = Methotrexate)

- ATC2 = GENERAL NUTRIENTS
- ATC2 = VITAMINS
- ATC2 = CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, if used before Day 15
- Preferred Drug Name = Tacrolimus, if used before Day 15
- Preferred Drug Name = Pimecrolimus, if used before Day 15

2. Require to adjudicate rescue treatment
   - All other medications (not noted in 1. above) given for indications consistent with AD[1]
   - Medications noted in 1a above, when given for indications not consistent with AD

[1] Below is a list of indications consistent with AD based on PT level from concomitant medication/procedure data using MedDRA 18.0

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
General disorders and administration site conditions	General signs and symptoms NEC	Xerosis	10048222
Infections and infestations	Bacterial infections NEC	Bacterial infection	10060945
Infections and infestations	Bacterial infections NEC	Eczema impetiginous	10051890
Infections and infestations	Bacterial infections NEC	Skin bacterial infection	10052891
Infections and infestations	Herpes viral infections	Eczema herpeticum	10014197
Infections and infestations	Herpes viral infections	Herpes simplex	10019948
Infections and infestations	Skin structures and soft tissue infections	Dermatitis infected	10012470
Infections and infestations	Skin structures and soft tissue infections	Eczema infected	10014199
Infections and infestations	Skin structures and soft tissue infections	Impetigo	10021531
Infections and infestations	Skin structures and soft tissue infections	Pyoderma	10037632
Infections and infestations	Skin structures and soft tissue infections	Rash pustular	10037888
Infections and infestations	Skin structures and soft tissue infections	Skin infection	10040872
Infections and infestations	Skin structures and soft tissue	Subcutaneous abscess	10042343

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
	infections		
Infections and infestations	Staphylococcal infections	Staphylococcal infection	10058080
Infections and infestations	Staphylococcal infections	Staphylococcal skin infection	10066409
Infections and infestations	Viral infections NEC	Kaposi's varicelliform eruption	10051891
Injury, poisoning and procedural complications	Skin injuries NEC	Excoriation	10049796
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Dry skin	10013786
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Pain of skin	10033474
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Skin disorder	10040831
Skin and subcutaneous tissue disorders	Dermal and epidermal conditions NEC	Skin fissures	10040849
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis	10012431
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis atopic	10012438
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Eczema	10014184
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Neurodermatitis	10029263
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Seborrhoeic dermatitis	10039793
Skin and subcutaneous tissue disorders	Erythemas	Erythema	10015150
Skin and subcutaneous tissue disorders	Erythemas	Plantar erythema	10051170
Skin and subcutaneous tissue disorders	Exfoliative conditions	Dermatitis exfoliative	10012455
Skin and subcutaneous tissue disorders	Pruritus NEC	Pruritus	10037087
Skin and subcutaneous tissue disorders	Rashes, eruptions and exanthems NEC	Rash	10037844
Skin and subcutaneous tissue disorders	Urticarias	Urticaria	10046735
Surgical and medical procedures	Analgesia supportive care	Pain management	10056350
Surgical and medical procedures	Hormonal therapeutic procedures NEC	Steroid therapy	10062117
Surgical and medical procedures	Therapeutic procedures NEC	Salvage therapy	10068833

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. DOI: 10.1056/NEJMoa1610020

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Indiana: Scott Guenthner, The Indiana Clinical Trials Center, Plainfield

Maryland: Benjamin Lockshin, DermAssociates, Rockville

Massachusetts: Alexa Kimball, Massachusetts General Hospital, Boston; David Rosmarin, Tufts Medical Center, Boston

Michigan: Tina Pickett-Baisden, Detroit Clinical Research Center, Farmington Hills

Minnesota: Philip Halverson, Clinical Research Institute, Inc., Plymouth; Harold Kaiser, Clinical Research Institute, Inc., Minneapolis

Missouri: Ann Martin, Washington University School of Medicine in St. Louis, St. Louis; Melody Stone, MediSearch Clinical Trials, St. Joseph

Montana: Kathleen Davis, Billings Clinic, Billings

Nevada: Vincent Mirkil, Clinical Research Consortium, Las Vegas

New Jersey: Robert Nossa, The Dermatology Group, Verona

New Mexico: Elizabeth Bretton, Albuquerque Clinical Trials, Inc., Albuquerque

New York: Andrew Alexis, Mt Sinai St. Luke's/Roosevelt Hospital Center, New York; Emma Guttman-Yassky, Icahn School of Medicine at Mount Sinai, New York; Marina Peredo, Jeffrey Weinberg, Forest Hills Dermatology Group, Forest Hills

North Carolina: Alan Fleischer, Wake Forest University Health Sciences, Winston-Salem; Rosalyn George, Wilmington Dermatology Center, Wilmington; Aida Lugo-Somolinos, University of North Carolina - School of Medicine, Chapel Hill; Adnan Nasir, Wake Research Associates, Raleigh

Oklahoma: Iftikhar Hussain, Vital Prospects Clinical Research, Tulsa

Oregon: Andrew Blauvelt, Oregon Medical Research Center, Portland; Eric Simpson, Oregon Health & Science University, Portland

Pennsylvania: Marvin Kalafer, Clinical Trial Center, LLC, Jenkintown

South Carolina: Marta Hampton, Roper St. Francis Healthcare, Charleston; John M. Humeniuk, Radiant Research, Greer; Ned Rupp, National Allergy and Asthma Research, LLC, Charleston

Texas: Daniel Carrasco, Austin Dermatology Associates, P.A., Austin; Brian MacGillivray, DCT-Stone Oak, LLC dba Discovery Clinical Trials, San Antonio; Angela Moore, Arlington Research Center, Inc., Arlington; Craig Teller, Bellaire Dermatology Associates (BDA), Bellaire; Stephen Tyring, Center for Clinical Studies, Webster

Utah: Duane Harris, Intermountain Clinical Research, Draper

Washington: Peter Jenkin, Dermatology Associates, Seattle

Drug Administration

Study drug (dupilumab or placebo) was administered subcutaneously weekly for 16 weeks (baseline [week 0] to week 15) following a 35-day screening and washout period. Patients assigned to receive dupilumab every other week alternated dupilumab injections with matching placebo in order to preserve the blind. Patients could choose to self-administer study drug (or have it administered by a caregiver) outside the clinic off-site during the weeks in which no clinic visits were scheduled. Patients and/or caregivers were trained by study staff; study staff administered the first dose and the patient or caregiver administered the second under the supervision of the study staff, followed by supervised self-administration at visits 2–4 in the clinic. Patients who preferred to have the study drug administered by study staff could have all doses administered in the clinic.

Post-Treatment Follow-Up

During the 16-week treatment period, patients had weekly study visits (some visits could be conducted by telephone). Clinical assessments were performed, safety was assessed, and blood samples were collected at specified clinic visits. At the end of the treatment period, eligible patients (who had achieved an Investigator's Global Assessment [IGA] score of 0 or 1 or ≥75% improvement from baseline in the Eczema Area Severity Index score [EASI-75] at week 16 with no rescue therapy) could enter a maintenance study (LIBERTY AD SOLO-CONTINUE; R668-AD-1415; NCT02395133); if they chose not to participate in the maintenance study, they could opt to enroll in an open-label extension study (LIBERTY AD MAINTAIN; R668-AD-1225; NCT01949311) but no earlier than 36 weeks after week 16. Patients ineligible for the maintenance study entered a safety follow-up period of at least 4 weeks after week 16 through week 28. Starting at week 20 they were eligible to enroll in the open-label extension study if

they had an IGA score of ≥3; patients with an IGA score of <3 continued follow-up to week 28 or until they had an IGA score of 3 or 4, whichever occurred first.

Rescue Treatments

If medically necessary (i.e., to control unacceptable atopic dermatitis symptoms), rescue treatment for atopic dermatitis with otherwise prohibited medications could be provided to study patients at the discretion of the investigator. For the purpose of efficacy analysis, patients who received rescue treatment during the study treatment period were considered treatment failures, but they could continue study treatment if rescue treatment consisted of topical medications (e.g., topical corticosteroids, topical calcineurin inhibitors). Topical calcineurin inhibitors were to be reserved for problem areas only, e.g., face, neck, intertriginous and genital areas, etc. If possible, investigators were to attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only in patients who did not respond adequately after at least 7 days of topical treatment. If a patient received rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study treatment was to be immediately discontinued. After treatment with these medications was completed, study treatment could be resumed if deemed appropriate by the investigator and the medical monitor, but no earlier than 5 half-lives after the last dose of systemic rescue medication. All patients were to complete the schedule of study visits and assessments whether or not they completed study treatment, and whether or not they received rescue treatment for atopic dermatitis. Investigators were to make every attempt to conduct efficacy and safety assessments (e.g., disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit could be used for this purpose if necessary.

Detailed Inclusion Criteria

- Male or female, ≥18 years of age
- Chronic atopic dermatitis (according to American Academy of Dermatology Consensus Criteria[1]) that has been present for ≥3 years before screening
- EASI score of ≥16 at screening and baseline
- IGA score of ≥3 (on a scale of 0–4, in which 3 is moderate and 4 is severe) at screening and baseline
- ≥10% body-surface area of atopic dermatitis involvement at screening and baseline
- Baseline pruritus numerical rating scale average score for maximum itch intensity of ≥3, based on the average of daily pruritus numerical rating scale scores for maximum itch intensity reported during the 7 days prior to randomization
- Documented recent history (within 6 months prior to screening) of inadequate response to treatment with topical medications, or patients for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks)
    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0 [indicating clear] to 2 [indicating mild] despite treatment with a daily regimen of topical corticosteroids of medium to higher potency (with or without topical calcineurin inhibitors as appropriate), applied for ≥28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent topical corticosteroids), whichever is shorter
    - Patients with documented systemic treatment for atopic dermatitis in the preceding 6 months are also considered to be 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 re-screened after such documentation is obtained (i.e., patients are shown to fail a 28-day course of mid-to-higher potency topical corticosteroids [with or without topical calcineurin inhibitors]).
- Has applied a stable dose of topical emollient (moisturizer) twice daily for ≥7 consecutive days immediately before the baseline visit
- Is willing and able to comply with all clinic visits and study-related procedures
- Is able to understand and complete study-related questionnaires
- Provides signed informed consent

Detailed Exclusion Criteria

- Participation in a prior dupilumab study
- Treatment with an investigative drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before baseline
- Treatment with immunosuppressive/immunomodulatory drugs or phototherapy for atopic dermatitis within 4 weeks of baseline, or any condition that, in the opinion of the investigator, was likely to require such treatment(s) during the first 4 weeks of study treatment
- Treatment with topical corticosteroids or topical calcineurin inhibitors within 1 week of baseline
- Treatment with biologics as follows:
    - Any cell-depleting agents including, but not limited to, rituximab: within 6 months prior to baseline visit, or until lymphocyte count returns to normal, whichever is longer
    - Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer
- Initiation of treatment of atopic dermatitis with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue to use stable doses of such moisturizers if initiated before the screening visit)
- Regular use (≥2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit
- Planned or anticipated use of any prohibited medications and procedures during study treatment
- Treatment with a live (attenuated) vaccine within 12 weeks prior to the baseline visit
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to the baseline visit, or

superficial skin infections within 1 week prior to the baseline visit. NOTE: patients may be rescreened after infection resolves

- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
- Positive for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody at the screening visit
- At baseline, presence of any conditions listed as criteria for study drug discontinuation
- Presence of skin comorbidities that may interfere with study assessments
- History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, and completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization
- History of alcohol or drug abuse within 2 years before the screening visit
- Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study
- Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may 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 the study, 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, case report forms, etc.)

- Planned or anticipated major surgical procedure during the patient's participation in this study
- Membership of the investigational team or his/her immediate family
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
- Women unwilling to use adequate birth control, if of reproductive potential and sexually active
- For further details, please see the study protocol posted at NEJM.org

Prohibited Concomitant Medications and Procedures

- Treatment with the following concomitant medications is prohibited during the study
  - Treatment with a live (attenuated) vaccine
  - Treatment with immunomodulating biologics
  - Treatment with an investigational drug (other than dupilumab)
  - Treatment with topical corticosteroids or topical calcineurin inhibitors; such agents could be administered during the study only if required for atopic dermatitis rescue. If topical corticosteroids and/or topical calcineurin inhibitors were used during the study, study treatment could continue as planned
  - Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), except if required for atopic dermatitis rescue, or if critically medically needed to treat concurrent medical conditions (e.g., asthma)
- Study drug will be discontinued if any of the following are used through week 16
  - Treatment with a live (attenuated) vaccine
  - Treatment with an investigational drug (other than dupilumab)
  - Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

NOTE: If a patient receives treatment with systemic corticosteroids or other systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), study treatment will be discontinued immediately. After treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the

investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication

- The following concomitant procedures are prohibited during study participation
  - Major elective surgical procedures
  - Phototherapy
  - Tanning in a bed/booth

Efficacy Outcomes to the Studies

- Key secondary end points
  - Proportion of patients with EASI-75 at week 16 (in countries in which this is not a coprimary end point)
  - Proportion of patients with ≥4-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 16
  - Proportion of patients with ≥3-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 16
  - Percent change from baseline to week 16 in weekly average of peak daily pruritus numerical rating scale score
  - Proportion of patients with ≥4-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 4
  - Proportion of patients with ≥4-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 2
- Other secondary end points
  - Change in weekly average of peak daily pruritus numerical rating scale score from baseline to week 16
  - Percent change in EASI score from baseline to week 16
  - Proportion of patients with improvement from baseline of ≥50% in EASI score (EASI-50) at week 16
  - Proportion of patients with improvement from baseline of ≥90% in EASI score (EASI-90) at week 16
  - Change from baseline to week 16 in percent body-surface area affected

  - Percent change from baseline to week 16 in Scoring Atopic Dermatitis (SCORAD) score
  - Change from baseline to week 16 in Dermatology Life Quality Index (DLQI) total score
  - Change from baseline to week 16 in Patient-Oriented Eczema Measure (POEM) total score
  - Change from baseline to week 16 in Hospital Anxiety and Depression Scale (HADS) total score
  - Percent change from baseline to week 16 in Global Individual Signs Score (GISS)
  - Percent change from baseline to week 2 in weekly average of peak daily pruritus numerical rating scale score
  - Incidence of skin infection adverse events requiring systemic treatment from baseline through week 16
  - Incidence of serious adverse events from baseline through week 16
  - Incidence of adverse events leading to treatment discontinuation from baseline through week 16
- Additional secondary end points
  - Proportion of patients with HADS anxiety (HADS-A) and HADS depression (HADS-D) subscores of <8 at week 16, among patients with HADS-A or HADS-D score of ≥8 at baseline
  - Proportion of patients with ≥4-point improvement in POEM total score
  - Proportion of patients with ≥4-point improvement in DLQI total score
- Additional efficacy end points
  - Change and percent change from baseline to week 16 in EuroQol 5-Dimension Health Questionnaire score[2]

- Proportion of patients who respond “absence of pruritus” or “mild pruritus” in the Pruritus Categorical Scale at week 16[3]
- Proportion of patients who respond “very good” or “excellent” in the Patient Global Assessment of Disease Status at week 16
- Proportion of patients who respond “very good” or “excellent” in the Patient Global Assessment of Treatment Effect at week 16
- Proportion of patients who achieve a reduction in the IGA score of ≥2 from baseline to week 16
- Proportion of patients who achieve a reduction in the IGA score of ≥3 from baseline to week 16
- Assessment of sick leave/missed school days

Additional Statistical Methods

Multiple imputation analyses

Multiple imputation with an analysis of covariance (ANCOVA) model was the primary analysis for continuous variables. Patients' efficacy data through week 16 after rescue medication usage were set to missing first, and then were imputed by the multiple imputation method. Missing data from the full analysis set were imputed 50 times to generate 50 complete data sets by using the Statistical Analysis System (SAS) procedure "MI" following the two steps below:

Step 1: The monotone missing pattern was induced by Markov Chain Monte Carlo (MCMC) method in the "MI" procedure. The monotone missing pattern means that if a patient had a missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits were imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, randomization strata (region, disease severity), and relevant baseline.

The week-16 data of each of the 50 complete data sets were analyzed using an ANCOVA model with treatment, randomization strata (region, disease severity), and relevant baseline values included in the model, and the SAS MIANALYZE procedure was used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula.

The multiple imputation model included:

- the covariates included in the ANCOVA model, including treatment group, baseline values, and randomization strata
- measured end point values from every clinic visit up to week 16

Categorical variables included in the above model (i.e., treatment group and randomization strata) were not expected to be missing.

To account for the impact of rescue medication on the efficacy effect for continuous end points, the data collected after rescue medication was initiated were treated as missing.

Methods for sensitivity analysis of efficacy outcomes

For binary outcomes, prespecified sensitivity analyses were all performed using the Cochran–Mantel–Haenszel test after various missing data-handling approaches described as follows:

1. Last observation carried forward (LOCF) for imputation of missing data, with patients after rescue treatment or patients withdrawing from the study considered as non-responders
2. All observed values regardless of rescue treatment or study withdrawal; patients with missing data treated as non-responders
3. All observed values regardless of rescue treatment or study withdrawal; missing data were not imputed

For continuous end points, prespecified sensitivity analyses were as follows:

1. Multiple imputation using all observed data regardless of rescue medication use or if data were collected after withdrawal

2. Mixed-effect repeated-measures model with data collected after rescue medication use treated as missing. The model included factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the within-patient errors. Denominator degrees of freedom were estimated using approximation of SATTERTH. The efficacy data were set to missing after rescue medication was used. No imputation was made
3. Data collected after rescue medication use treated as missing, followed by the LOCF method and ANCOVA model, using the treatment group, baseline value, and randomization strata
4. Data collected after rescue medication use treated as missing, followed by worst observation carried forward method and ANCOVA using the treatment group, baseline value, and randomization strata
5. ANCOVA model using study, treatment group, baseline value, and randomization strata; efficacy data were based on all observed values, regardless of rescue medication use, without imputation.

Sample size and power

To detect a 29% difference between dupilumab and placebo treatment in the proportion of patients achieving the primary end point of the proportion of patients achieving an IGA score of 0 or 1 at week 16, assuming the percentages are 38% and 9% for dupilumab and placebo, respectively, the enrollment of 55 patients per group provided 90% power. However, to provide sufficient safety data and ensure sufficient responders for the maintenance study, the sample size was increased to 600 patients in total for each study, with a randomization ratio of 1:1:1 dupilumab 300 mg weekly:dupilumab 300 mg every other week:placebo. It was estimated that with 200 patients per group, this would provide 99% power in both comparisons (between dupilumab 300 mg weekly and placebo, and between dupilumab 300 mg

every other week and placebo). The same number of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

To control for the overall type-1 error rate at 0.05 for primary and secondary end points across dose regimens, in consideration of multiplicity, a significance level of 0.025, two-sided, was used for comparisons of each dupilumab dose group with placebo, according to a prespecified hierarchical order. Statistical significance of differences between the dose groups was not investigated.

An additional power calculation was based on the secondary end point "proportions of patients with improvement of weekly average of peak daily pruritus numerical rating scale score of ≥4 from baseline to week 16"; as the analysis includes patients with baseline peak pruritus numerical rating scale score of ≥4, and assuming that 180 such patients would be randomized into each treatment group, with responder rates of 39% and 9% for dupilumab and placebo, respectively, the analysis can provide 99% power at a level of 0.025 from each comparison.

Analysis sets

Efficacy analyses were carried out using the full analysis set, which included all randomized patients. For the proportion of patients with a 3- or 4-point improvement in peak pruritus numerical rating scale score, the analysis was conducted only in patients with baseline pruritus numerical rating scale score of ≥3 or numerical rating scale score of ≥4, respectively. For the proportions of patients achieving a ≥4-point improvement in DLQI or POEM score from baseline, the analysis was carried out only in patients with baseline DLQI or POEM total score of ≥4. For the proportion of patients achieving a HADS-A and HADS-D score of <8, the analysis was carried out only in patients with baseline HADS-A or HADS-D score

of ≥8. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug.

Narratives of Patient Deaths

Overview: There were two deaths in the dupilumab groups in SOLO 2. The detailed patient narratives are provided here.

Patient 1: Female patient, 49 years of age

DESCRIPTION OF EVENTS QUALIFYING FOR REPORTING IN THE NARRATIVE

On study day 170 (October 23, 2015), the patient had serious adverse events of severe intensity, reported as asthma attack (asthma), anoxic encephalopathy (hypoxic-ischemic encephalopathy), and respiratory failure (respiratory failure). The events were serious because they required hospitalization, were considered life-threatening, and resulted in death. The patient died on November 11, 2015 (study day 189) due to these events. The investigator's assessment of causality was "not related" to study drug.

NARRATIVE

The investigational product (IP subcutaneous) had been started on May 7, 2015. The most recent dose of IP before the event was on August 19, 2015 (study day 105). At that time, the patient had received a total of 16 doses of study drug (8 doses of 300 mg dupilumab every other week and 8 doses of placebo every other week on alternate weeks). At the time of the event, the patient was in follow-up and no longer receiving IP.

The patient had a history of asthma since 1990. The only recorded therapy for asthma until October 22, 2015, was an albuterol inhaler and albuterol as a nebulizer at home. The patient had taken two

nonsteroidal anti-inflammatory drugs for sciatica since July 2015; naproxen was taken constantly and ibuprofen as needed. Valproic acid was started in 1990 for bipolar disorder. The patient had been a smoker for 30 years.

On October 22, 2015, the patient received a Benadryl® (diphenhydramine) injection for itching from her primary care physician. The patient had an asthma attack flare-up at this time. During the visit, the patient was coughing and wheezing and received Qvar® (beclomethasone dipropionate HFA). The patient was seen for follow-up for eczema but complained of cough for 5 days. The patient had used her albuterol nebulizer at home without any effect.

On October 23, 2015 (study day 170), 5 months after the first IP administration (and approximately 2 months after the last IP administration), the patient experienced serious adverse events of asthma, hypoxic–ischemic encephalopathy, and respiratory failure, all of severe intensity. The events were considered life-threatening and eventually resulted in death. On that day, the patient awoke very short of breath with a cough and had no improvement with the use of an inhaler. The patient stood up to breathe better and became pale, turned blue, and lost consciousness. The patient was apneic for 2 minutes prior to emergency-personnel arrival. The patient lost pulse twice. Epinephrine was administered twice. The patient had an initial gain of pulse but was found in asystole in the emergency room. The patient was admitted to the hospital because of a life-threatening asthma attack. The patient arrived intubated and ventilated. The patient was experiencing the events asthma attack, cardiac arrest, and respiratory arrest, all considered severe in intensity.

The patient developed seizures and was in a medically induced coma because she was fighting the ventilator.

During hospitalization, the patient was treated with saline, norepinephrine, glucose, insulin, famotidine, valproate semisodium, fentanyl, acetylsalicylic acid, white petrolatum ophthalmic ointment, pantoprazole sodium, fentanyl-NS, ipratropium bromide/salbutamol sulfate, methylprednisolone sodium succinate, vecuronium, and propofol.

On October 25, 2015, 2 days after the onset of the asthma attack, the following tests were reported: urine analysis — 3 white blood cells and 7 epithelial cells; chest X-ray — no acute infiltrate; venous Doppler — no evidence of deep-vein thrombosis (DVT); methicillin-resistant *Staphylococcus aureus* screen — negative; computed tomography (CT) — no obvious infarct or mass; respiratory culture from endotracheal aspirate — heavy growth of *S. aureus*; moderate positive cocci.

On October 27, 2015, the following tests were reported: transthoracic echocardiogram — normal left ventricular size with mildly reduced systolic function with estimated ejection fraction of 45–50%; hypokinesia of the apex and apical septum; no hemodynamically significant valvular pathology appreciated.

On October 28, 2015, the following test was reported: CT head — no intracranial hemorrhage.

On November 2, 2015, the following test was reported: abdomen ultrasound — hepatomegaly.

On unspecified dates, a duplex ultrasound was negative for DVT, a chest X-ray was negative for cardiopulmonary disease, and an echocardiogram showed overall normal size of left ventricle with severely reduced ejection fraction of 30% and severe hypokinesis of anterior and anteroseptal wall, posterior wall, and akinetic apex.

On November 11, 2015 (study day 189), the patient died due to anoxic encephalopathy, respiratory failure, asthma exacerbation, and asthma.

The investigator considered the events to be not related to IP. The investigator's alternative explanation for the events was underlying/concomitant illness.

Relationship to IP according to Company for all events: excluded.

Patient 2: Male patient, 31 years of age

DESCRIPTION OF EVENTS QUALIFYING FOR REPORTING IN THE NARRATIVE

On study day 93 (August 6, 2015), the patient had a serious adverse event of severe intensity, reported as suicide (completed suicide). The event was serious because it resulted in death. The patient died on August 6, 2015, due to this event. The investigator's assessment of causality was "not related" to study drug.

NARRATIVE

On April 29, 2015, during the screening visit, the investigator reported that the patient made no mention of a history of depression, suicide attempt, or suicidal ideation during the medical history or concomitant medication review. On May 5, 2015, at the baseline visit, the patient was questioned about his mental health history, and he reported that depression had been present since autumn 2014 and was primarily caused by his severe atopic dermatitis. Medical records obtained from the patient's primary physician indicated a history of new depression and suicidal ideation (November 14, 2014). It was also noted that the patient had a family history of suicide (grandmother). The patient reported a brief hospitalization for acute worsening of depression and a request for a referral for mental health counseling during a visit to his primary physician on November 26, 2014 (dates of hospitalization not provided, and patient reported he was doing much better).

The first dose of IP (subcutaneous) was on May 6, 2015. The most recent dose of IP before the event was on July 29, 2015 (study day 85). At that time, the patient had received a total of 13 doses of 300 mg dupilumab weekly.

On August 11, 2015, the patient's sister called to inform the site that the patient died from an intentional overdose of drugs on August 6, 2015 (study day 93), 3 months after the first IP administration, and 8 days after the last dose administration. The event was assessed as an adverse event of special interest and was considered severe in intensity.

The death certificate noted the cause of death as acute mixed-drug intoxication due to the combined effects of valproic acid and diphenhydramine. Another condition contributing to death was noted as dilated cardiomyopathy (noted in the death certificate). The description of how the injury occurred was noted as an intentional acute drug intoxication. In addition, the death certificate specified that there was no injury at work and tobacco use did not contribute to death.

Action taken with study drug was reported as "dose not applicable".

The investigator considered the event to be not related to IP. The causality rationale was noted, as the patient's family attributed the depression and suicide to lifelong, severe chronic atopic dermatitis. Based on statements made by the patient (to the investigator at the baseline visit) and discussion with the patient's family, the investigator believed the patient's severe, chronic atopic dermatitis was the primary contributing factor to his depression and suicide.

Relationship to IP according to Company: not related to study drug or study procedure, but likely related to patient's past medical history of depression.

Table S1. Efficacy End Points[4]

End Point	Description	Range	MCID
Eczema Area and Severity Index (EASI)[5,6]	Assesses severity and body surface area affected by erythema, induration/papulation/edema, excoriations, and lichenification, which are graded systematically for each anatomical region and assembled in a composite score	0–72*	6.6
Investigator's Global Assessment (IGA)[7]	Determines severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe)	0–4*	n/a
Pruritus numerical rating scale (NRS)[8]	Two single-item 11-point scales that assess maximum and average intensity of itch within the previous 24 hours. Psychometric validation data submitted to the US Food and Drug Administration (FDA) provide evidence that this is a well-defined, reliable, sensitive, and valid scale (data on file). Responder analyses submitted to the FDA suggest that the most appropriate definition of a responder on the	0–10*	n/a

	peak pruritus numerical rating scale is in the range of 3 to 4 points		
Scoring Atopic Dermatitis (SCORAD)[6,9]	The extent and severity of atopic dermatitis over the body area (A) and the severity of 6 specific symptoms (erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness) (B) are assessed and scored by the investigator. Subjective assessment of itch and sleeplessness is scored by the patient (C). The SCORAD score is a combined score (A/5 + 7B/2 + C) of body area affected, and investigator and patient symptom scoring, with a maximum of 103	0–103*	8.7
Global Individual Signs Score (GISS)	Individual components of the atopic dermatitis lesions (erythema, infiltration/papulation, excoriations, and lichenification) were rated globally (i.e., 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. The cumulative score, which ranges from 0 to 12, is the sum of the four components	0–12*	n/a
Patient-Oriented Eczema Measure	A 7-item, validated questionnaire used in clinical practice and clinical	0–28*	4

(POEM)[6,10]	trials to assess time spent with disease symptoms in children and adults, and their impact on sleep		
Dermatology Life Quality Index (DLQI)[11,12]	A 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of skin conditions on quality of life	0–30*	4
Hospital Anxiety and Depression Scale (HADS)[13,14]	A general Likert scale used to detect states of anxiety and depression; anxiety and depression subscales each with 7 items	0–42 for total score; 0–21 for each subscale*	n/a

* Higher scores indicate greater severity/worsened state.
MCID, minimum clinically important difference; n/a, not applicable.
Adapted from: The Lancet, Vol. 387, Thaçi D, Simpson EL, Beck LA, et al., Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial, Pages 40-52, Copyright (2016), with permission from Elsevier.

Table S2. Additional Baseline Characteristics

	SOLO 1			SOLO 2		
Variable	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
Peak pruritus numerical rating scale score ≥3 — no. (%)	221 (99)	220 (98)	211 (95)*	226 (96)	231 (99)*	234 (98)
Peak pruritus numerical rating scale score ≥4 — no. (%)	212 (95)	213 (95)	201 (90)	221 (94)	225 (97)	228 (95)

Peak pruritus numerical rating scale score is a patient-reported measure which assesses maximum itch intensity in the previous 24 hours using a 10-point scale (from 0 [no itch] to 10 [worst itch imaginable]).[8]

* P<0.05 vs. placebo.

Table S3. Prior Systemic Medication Ended Prior to Baseline (Safety Analysis Set)

	SOLO 1			SOLO 2		
Prior systemic therapy — no. (%)	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Systemic corticosteroids	78 (35)	77 (34)	65 (30)	82 (35)	80 (34)	73 (31)
Immunosuppressants	52 (23)	60 (26)	61 (28)	70 (30)	77 (33)	75 (32)
Calcineurin inhibitors	40 (18)	47 (21)	49 (23)	53 (23)	60 (25)	52 (22)
Selective immunosuppressants	8 (4)	14 (6)	9 (4)	4 (2)	10 (4)	9 (4)
Other immunosuppressants	20 (9)	24 (11)	23 (11)	25 (11)	27 (11)	28 (12)
Interleukin inhibitors	3 (1)	2 (1)	0	0	0	1 (<1)
Tumor necrosis factor-	1 (1)	2 (1)	0	0	1 (<1)	0

	SOLO 1			SOLO 2		
Prior systemic therapy — no. (%)	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
alpha inhibitors						

Table S4. Additional Efficacy Outcomes (Not Included in Hierarchical Testing)

	SOLO 1			SOLO 2		
End Point	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
DLQI score, ≥4-point improvement from baseline to week 16 — no. (%)*	65 (31)	134 (64) †	122 (58) †	62 (28)	163 (73) †	145 (62) †
POEM score, ≥4-point improvement from baseline to week 16 — no. (%)‡	60 (27)	150 (68) †	140 (63) †	57 (24)	167 (72) †	153 (64) †
HADS-A and HADS-D score <8 at week 16 — no./N (%)§	12/97 (12)	41/100 (41) †	37/102 (36) †	7/115 (6)	51/129 (40) †	56/136 (41) †

* In the subset of patients with DLQI ≥4 at baseline.

† Nominal P<0.001 vs. placebo.
‡ In the subset of patients with POEM ≥4 at baseline.
§ In the subset of patients with HADS-A or HADS-D ≥8 at baseline, representing the cutoff for identifying patients with anxiety or depression, respectively.
Scores on the DLQI range from 0 to 30, with higher scores indicating greater impact on quality of life; a change of 4 has been estimated as the minimal clinically important difference (MCID).[11,12] Scores on the POEM range from 0 to 28, with higher scores indicating greater symptom burden; a change of 4 has been estimated as the MCID.[6,10] HADS total score ranges from 0 to 42 (HADS-A and HADS-D subscale scores range from 0 to 21)[13,14] with higher scores indicating greater burden of anxiety and depression symptoms; the MCID for this scale has not been determined. Based on Bjelland et al.,[13] an optimal balance between sensitivity and specificity for HADS as a screening instrument was achieved most frequently at a cutoff score of ≥8 for both HADS-A and HADS-D, giving sensitivities and specificities for both subscales of approximately 0.80. Receiver-operator characteristic curves also identified scores of ≥8 to be an optimal cutoff score for caseness for both anxiety disorders and depression based on the International Classification of Diseases, Ninth Revision (ICD-9). Most outcomes were assessed at scheduled study visits. DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety subscore; HADS-D, HADS depression subscore; N, number of patients in baseline subgroup; POEM, Patient-Oriented Eczema Measure.

Table S5. Proportion of Patients Receiving Rescue Therapy at Week 16 (Full Analysis Set)

	SOLO 1			SOLO 2		
	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
Rescue therapy — no. (%)						
Any rescue therapy	115 (51)	47 (21)	52 (23)	123 (52)	35 (15)	49 (21)
Systemic corticosteroids	17 (8)	2 (1)	5 (2)	30 (13)	3 (1)	6 (3)
Immunosuppressants	5 (2)	3 (1)	2 (1)	16 (7)	1 (<1)	2 (1)
Calcineurin inhibitors	4 (2)	2 (1)	1 (<1)	13 (6)	1 (<1)	2 (1)
Selective immunosuppressants	0	1 (<1)	1 (<1)	0	0	0
Other	1 (<1)	0	0	4 (2)	0	0

	SOLO 1			SOLO 2		
	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
immunosuppressants						

Table S6. Sensitivity Analyses of Primary Outcome and Key Secondary Outcomes

	SOLO 1			SOLO 2		
End Point	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
Primary analysis						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — no. (%)	23 (10)	85 (38)*	83 (37)*	20 (8)	84 (36)*	87 (36)*
EASI-75 at week 16 — no. (%)†	33 (15)	115 (51)*	117 (52)*	28 (12)	103 (44)*	115 (48)*
Sensitivity analysis 1: All observed values regardless of rescue treatment; missing considered as non-responder						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — no. (%)	29 (13)	91 (41)*	85 (38)*	25 (11)	87 (37)*	91 (38)*
EASI-75 at week 16 — no. (%)	50 (22)	133 (59)*	136 (61)*	37 (16)	116 (50)*	138 (58)*
Sensitivity analysis 2: Last observation carried forward; patient considered as non-responder after rescue treatment						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — no. (%)	25 (11)	85 (38)*	88 (39)*	22 (9)	86 (37)*	91 (38)*

	SOLO 1			SOLO 2		
End Point	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
EASI-75 at week 16 — no. (%)	38 (17)	122 (54)*	126 (57)*	32 (14)	108 (46)*	132 (55)*
Sensitivity analysis 3: All observed values regardless of rescue treatment; missing data not imputed						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — n/N1 (%)	29/205 (14)	91/216 (42)*	85/207 (41)*	25/219 (11)	87/224 (39)*	91/224 (41)*
EASI-75 at week 16 — no./N1 (%)	50/205 (24)	133/216 (62)*	136/207 (66)*	37/219 (17)	116/224 (52)*	138/224 (62)*

* P<0.001 vs. placebo.

† Co-primary outcome in EU and Japan. EASI, Eczema Area and Severity Index; EASI-75, ≥75% improvement in EASI score from baseline; IGA, Investigator's Global Assessment; n, number of patients; N1, number of patients without missing data at week 16.

Table S7. Serious Adverse Events (MedDRA PTs) (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
≥1 Serious adverse event	11 (5.0)	7 (3.1)	2 (0.9)	13 (5.6)	4 (1.7)	8 (3.4)
Acute myocardial infarction	0	1 (0.4)	0	0	0	1 (0.4)
Myocardial infarction	0	0	1 (0.5)	0	0	0
Coronary artery disease	1 (0.5)	0	0	0	0	0
Cardiac failure, congestive	0	0	0	0	0	1 (0.4)
Abdominal pain	0	0	0	0	0	1 (0.4)
Colonic pseudo-obstruction	0	0	0	0	0	1 (0.4)
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Kidney infection	0	0	1 (0.5)	0	0	0
Mastitis	1 (0.5)	0	0	0	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Urinary tract infection bacterial	1 (0.5)	0	0	0	0	0
Cellulitis	0	0	0	0	0	1 (0.4)
Erysipelas	0	0	0	0	0	1 (0.4)
Endocarditis bacterial	0	0	0	1 (0.4)	0	0
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Skin infection	0	0	0	1 (0.4)	0	0
Dermatitis atopic	3 (1.4)	2 (0.9)	0	5 (2.1)	0	1 (0.4)
Dermatitis exfoliative	0	0	0	0	1 (0.4)	0
Clavicle fracture	0	1 (0.4)	0	0	0	0
Laceration	0	1 (0.4)	0	0	0	0
Concussion	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Fall	0	0	0	0	1 (0.4)	0
Ligament sprain	0	0	0	1 (0.4)	0	0
Radius fracture	0	0	0	0	1 (0.4)	0
Cerebrovascular accident	0	0	0	1 (0.4)	0	0
Headache	0	0	0	0	1 (0.4)	0
Subarachnoid hemorrhage	0	0	0	0	1 (0.4)	0
Completed suicide	0	0	0	0	0	1 (0.4)
Delirium	0	0	0	0	0	1 (0.4)
Confusional state	0	0	0	1 (0.4)	0	0
Psychotic disorder	0	0	0	1 (0.4)	0	0
Depression	1 (0.5)	0	0	0	0	0
Suicidal ideation	2 (0.9)	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Lipoma	0	1 (0.4)	0	0	0	0
Hodgkin's disease	0	0	0	0	0	1 (0.4)
Nephrolithiasis	0	0	1 (0.5)	0	0	0
Limb operation	0	1 (0.4)	0	0	0	0
Anemia	1 (0.5)	0	0	0	0	0
Thrombocytopenia	0	0	0	1 (0.4)	0	0
Hyperglycemia	1 (0.5)	0	0	0	0	0
Failure to thrive	0	0	0	1 (0.4)	0	0
Intervertebral disc protrusion	1 (0.5)	0	0	0	0	0
Bursitis	0	0	0	1 (0.4)	0	0
Aortic stenosis	1 (0.5)	0	0	0	0	0
Abortion, spontaneous	0	0	0	0	0	1 (0.4)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Angle-closure glaucoma	0	0	0	1 (0.4)	0	0
Acute kidney injury	0	0	0	2 (0.9)	0	0

Serious adverse events were defined as any untoward medical occurrence that results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is an important medical event. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S8. Adverse Events (MedDRA PTs) Leading to Discontinuation (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
AEs leading to discontinuation	2 (0.9)	4 (1.7)	4 (1.8)	5 (2.1)	2 (0.8)	3 (1.3)
Dermatitis atopic	1 (0.5)	2 (0.9)	1 (0.5)	2 (0.9)	1 (0.4)	0
Dermatitis allergic	0	0	1 (0.5)	0	0	0
Lymphocytosis	0	0	1 (0.5)	0	0	0
Neutropenia	0	0	0	0	1 (0.4)	0
Diarrhea	0	0	0	0	0	1 (0.4)
Acute myocardial infarction	0	1 (0.4)	0	0	0	0
Conjunctivitis allergic	0	0	1 (0.5)	0	0	0
Angle-closure glaucoma	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Folliculitis	0	0	1 (0.5)	0	0	0
Eczema, impetiginous	0	0	0	0	1 (0.4)	0
Endocarditis bacterial	0	0	0	1 (0.4)	0	0
Sepsis	0	0	0	1 (0.4)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Hodgkin disease	0	0	0	0	0	1 (0.4)
Lethargy	0	0	0	0	0	1 (0.4)
Cerebrovascular accident	0	0	0	1 (0.4)	0	0
Clavicle fracture	0	1 (0.4)	0	0	0	0
Laceration	0	1 (0.4)	0	0	0	0
Suicidal ideation	2 (0.9)	0	0	0	0	0
Psychotic disorder	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Abortion, spontaneous	0	0	0	0	0	1 (0.4)
Acute kidney injury	0	0	0	1 (0.4)	0	0

Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. AE, adverse event, MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S9. Infections: Skin and non-Skin (MedDRA PTs) (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
Skin infections*	18 (8.1)	13 (5.7)	14 (6.4)	26 (11.1)	14 (5.9)	15 (6.3)
Eczema herpeticum	2 (0.9)	1 (0.4)	1 (0.5)	1 (0.4)	2 (0.8)	0
Impetigo	4 (1.8)	1 (0.4)	2 (0.9)	3 (1.3)	2 (0.8)	0
Skin infection	2 (0.9)	2 (0.9)	1 (0.5)	5 (2.1)	1 (0.4)	1 (0.4)
Infected dermal cyst	0	1 (0.4)	1 (0.5)	0	0	0
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Acne pustular	0	0	1 (0.5)	0	0	0
Rash pustular	0	0	0	1 (0.4)	0	1 (0.4)
Paronychia	1 (0.5)	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Soft tissue infection	1 (0.5)	0	0	0	0	0
Folliculitis	4 (1.8)	2 (0.9)	3 (1.4)	4 (1.7)	2 (0.8)	3 (1.3)
Cellulitis	2 (0.9)	1 (0.4)	1 (0.5)	2 (0.9)	0	2 (0.8)
Eczema impetiginous	0	0	1 (0.5)	1 (0.4)	3 (1.3)	1 (0.4)
Furuncle	0	2 (0.9)	1 (0.5)	1 (0.4)	0	0
Staphylococcal impetigo	0	1 (0.4)	0	0	0	0
Staphylococcal skin infection	0	1 (0.4)	0	2 (0.9)	0	1 (0.4)
Molluscum contagiosum	1 (0.5)	1 (0.4)	1 (0.5)	1 (0.4)	0	2 (0.8)
Otitis externa	0	0	1 (0.5)	0	2 (0.8)	0
Eyelid infection	0	0	1 (0.5)	0	0	0
Otitis externa fungal	0	0	1 (0.5)	0	0	0
Wound infection	0	0	1 (0.5)	0	1 (0.4)	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Tinea versicolor	1 (0.5)	1 (0.4)	0	0	0	1 (0.4)
Tinea pedis	2 (0.9)	0	0	0	0	0
Body tinea	0	0	0	0	0	1 (0.4)
Tinea manuum	0	0	0	1 (0.4)	0	0
Erysipelas	1 (0.5)	0	0	0	0	1 (0.4)
Skin bacterial infection	0	0	0	2 (0.9)	0	0
Subcutaneous abscess	0	0	0	3 (1.3)	1 (0.4)	0
Abscess limb	0	0	0	0	0	1 (0.4)
Non-skin infections	49 (22.1)	69 (30.1)	67 (30.7)	57 (24.4)	58 (24.6)	61 (25.7)
Nasopharyngitis	17 (7.7)	22 (9.6)	25 (11.5)	22 (9.4)	20 (8.5)	20 (8.4)
Upper respiratory tract infection	5 (2.3)	6 (2.6)	11 (5.0)	5 (2.1)	7 (3.0)	9 (3.8)
Conjunctivitis	2 (0.9)	11 (4.8)	7 (3.2)	1 (0.4)	9 (3.8)	9 (3.8)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Conjunctivitis bacterial	1 (0.5)	2 (0.9)	4 (1.8)	1 (0.4)	4 (1.7)	4 (1.7)
Oral herpes	4 (1.8)	9 (3.9)	4 (1.8)	4 (1.7)	8 (3.4)	9 (3.8)
Cystitis	0	1 (0.4)	3 (1.4)	0	2 (0.8)	0
Bacteriuria	0	0	2 (0.9)	1 (0.4)	1 (0.4)	0
Herpes simplex	3 (1.4)	7 (3.1)	2 (0.9)	1 (0.4)	0	1 (0.4)
Influenza	1 (0.5)	1 (0.4)	2 (0.9)	1 (0.4)	2 (0.8)	1 (0.4)
Otitis media	1 (0.5)	0	2 (0.9)	0	0	0
Pharyngitis	2 (0.9)	1 (0.4)	2 (0.9)	2 (0.9)	0	1 (0.4)
Tonsillitis	1 (0.5)	1 (0.4)	2 (0.9)	0	0	0
Asymptomatic bacteriuria	0	0	1 (0.5)	0	0	0
Bronchitis	2 (0.9)	2 (0.9)	1 (0.5)	2 (0.9)	1 (0.4)	2 (0.8)
Eye infection	0	2 (0.9)	1 (0.5)	0	0	1 (0.4)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Gastroenteritis	0	2 (0.9)	1 (0.5)	0	0	2 (0.8)
Herpes virus infection	0	0	1 (0.5)	1 (0.4)	0	0
Hordeolum	0	0	1 (0.5)	1 (0.4)	0	2 (0.8)
Kidney infection	0	0	1 (0.5)	0	0	0
Esophageal candidiasis	0	0	1 (0.5)	0	0	0
Ophthalmic herpes simplex	0	0	1 (0.5)	0	0	0
Sinusitis	1 (0.5)	2 (0.9)	1 (0.5)	5 (2.1)	0	0
Staphylococcal infection	0	0	1 (0.5)	0	0	0
Viral infection	0	0	1 (0.5)	0	0	0
Bacterial infection	0	1 (0.4)	0	0	0	0
Bacterial sepsis	0	1 (0.4)	0	0	0	0
Conjunctivitis viral	0	2 (0.9)	0	1 (0.4)	2 (0.8)	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Diverticulitis	0	1 (0.4)	0	0	0	0
Ear infection	0	1 (0.4)	0	0	0	0
Gastroenteritis norovirus	1 (0.5)	0	0	0	0	0
Gastroenteritis viral	2 (0.9)	0	0	1 (0.4)	1 (0.4)	0
Gastrointestinal infection	1 (0.5)	0	0	0	0	0
Genital herpes	1 (0.5)	0	0	0	0	1 (0.4)
Gingivitis	0	1 (0.4)	0	0	0	0
Herpes zoster	1 (0.5)	1 (0.4)	0	1 (0.4)	0	0
Mastitis	1 (0.5)	1 (0.4)	0	0	0	0
Pharyngitis streptococcal	0	2 (0.9)	0	0	0	3 (1.3)
Respiratory tract infection	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)
Rhinitis	2 (0.9)	1 (0.4)	0	0	2 (0.8)	1 (0.4)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Sialoadenitis	0	1 (0.4)	0	0	0	0
Urinary tract infection	4 (1.8)	2 (0.9)	0	4 (1.7)	2 (0.8)	2 (0.8)
Urinary tract infection bacterial	1 (0.5)	0	0	0	0	0
Viral upper respiratory tract infection	1 (0.5)	0	0	1 (0.4)	2 (0.8)	0
Ear infection bacterial	0	0	0	0	1 (0.4)	1 (0.4)
Herpes ophthalmic	0	0	0	1 (0.4)	0	1 (0.4)
Tooth infection	0	0	0	0	0	1 (0.4)
Acarodermatitis	0	0	0	1 (0.4)	0	0
Chronic tonsillitis	0	0	0	0	1 (0.4)	0
Dental gangrene	0	0	0	1 (0.4)	0	0
Endocarditis bacterial	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Herpes simplex otitis externa	0	0	0	0	1 (0.4)	0
Onychomycosis	0	0	0	1 (0.4)	0	0
Oral candidiasis	0	0	0	1 (0.4)	0	0
Periorbital abscess	0	0	0	1 (0.4)	0	0
Peritonsillar abscess	0	0	0	1 (0.4)	1 (0.4)	0
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Tooth abscess	0	0	0	1 (0.4)	0	0
Vaginal infection	0	0	0	1 (0.4)	0	0
Viral pharyngitis	0	0	0	1 (0.4)	0	0
Vulvovaginal candidiasis	0	0	0	2 (0.9)	0	0
Vulvovaginal mycotic infection	0	0	0	1 (0.4)	0	0

*Skin infections were adjudicated by the medical director for each study. Infections are listed as MedDRA PTs. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S10. Serious Infections, Severe Infections, and Opportunistic Infections (MedDRA PTs) (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
Serious infections and infestations	2 (0.9)	1 (0.4)	1 (0.5)	3 (1.3)	0	2 (0.8)
Kidney infection	0	0	1 (0.5)	0	0	0
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Mastitis	1 (0.5)	0	0	0	0	0
Bacterial urinary tract infection	1 (0.5)	0	0	0	0	0
Cellulitis	0	0	0	0	0	1 (0.4)
Erysipelas	0	0	0	0	0	1 (0.4)
Endocarditis bacterial	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Skin infection	0	0	0	1 (0.4)	0	0
Severe infections and infestations	4 (1.8)	3 (1.3)	1 (0.5)	4 (1.7)	1 (0.4)	0
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Conjunctivitis	0	1 (0.4)	0	0	0	0
Herpes simplex	0	1 (0.4)	0	0	0	0
Kidney infection	0	0	1 (0.5)	0	0	0
Mastitis	1 (0.5)	0	0	0	0	0
Nasopharyngitis	1 (0.5)	0	0	0	0	0
Pharyngitis	1 (0.5)	0	0	0	0	0
Soft tissue infection	1 (0.5)	0	0	0	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Conjunctivitis bacterial	0	0	0	0	1 (0.4)	0
Endocarditis bacterial	0	0	0	1 (0.4)	0	0
Folliculitis	0	0	0	2 (0.9)	0	0
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Opportunistic infections	3 (1.4)	2 (0.9)	1 (0.5)	2 (0.9)	2 (0.8)	0
Eczema herpeticum	2 (0.9)	1 (0.4)	1 (0.5)	1 (0.4)	2 (0.8)	0
Herpes zoster	1 (0.5)	1 (0.4)	0	1 (0.4)	0	0

Serious adverse events were defined as any untoward medical occurrence that results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is an important medical event. Severe adverse events were defined as those that produce significant impairment of functioning or incapacitation and are a definite hazard to the patient's health. Opportunistic infections were determined based on the 2015 consensus guidance by Winthrop et al.[15] Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S11. Mean and Median Changes From Baseline in Eosinophils (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Change from baseline (10^9 per liter)						
Week 4						
N	205	217	207	222	220	222
Mean (SD)	0 (0.495)	0.07 (0.584)	0.07 (0.525)	–0.02 (0.547)	0.11 (0.568)	0.13 (0.650)
Median	0	0	0	0	0	0
Q1, Q3	−0.15, 0.10	−0.10, 0.20	−0.10, 0.20	–0.20, 0.20	−0.10, 0.20	−0.20, 0.20
Week 8						
N	194	215	201	208	216	216
Mean (SD)	−0.13 (0.484)	0.06 (0.675)	0.02 (0.538)	–0.09 (0.620)	0.07 (0.596)	0.12 (0.853)

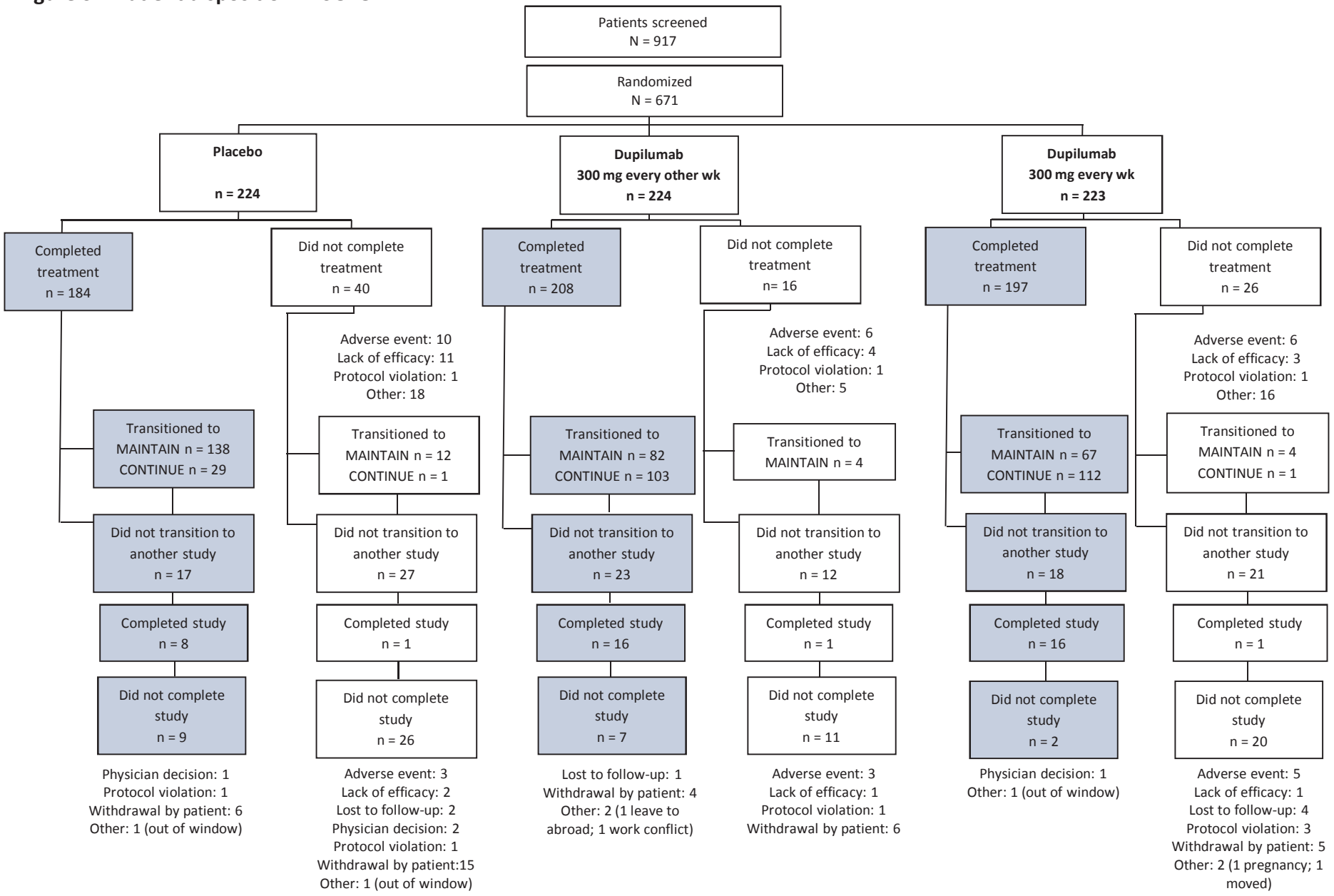
	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Median	−0.10	0	0	−0.05	0	0
Q1, Q3	−0.30, 0.10	−0.20, 0.20	−0.20, 0.20	−0.20, 0.10	−0.20, 0.20	−0.20, 0.20
Week 12						
N	191	212	196	207	219	218
Mean (SD)	−0.12 (0.443)	−0.01 (0.606)	0.01 (0.581)	−0.13 (0.675)	0.03 (0.545)	0.05 (0.591)
Median	−0.10	0	0	0	0	0
Q1, Q3	−0.30, 0.10	−0.20, 0.20	−0.20, 0.20	−0.20, 0.10	−0.20, 0.20	−0.20, 0.20
Week 16						
N	198	216	201	214	218	214
Mean (SD)	−0.16 (0.444)	−0.06 (0.568)	−0.01 (0.612)	−0.14 (0.591)	0.01 (0.641)	0.02 (0.573)
Median	−0.10	0	0	–0.10	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Q1, Q3	−0.30, 0	−0.25, 0.10	−0.20, 0.20	−0.30, 0.10	−0.20, 0.20	−0.30, 0.20

Q1, first quartile; Q3, third quartile; SD, standard deviation.

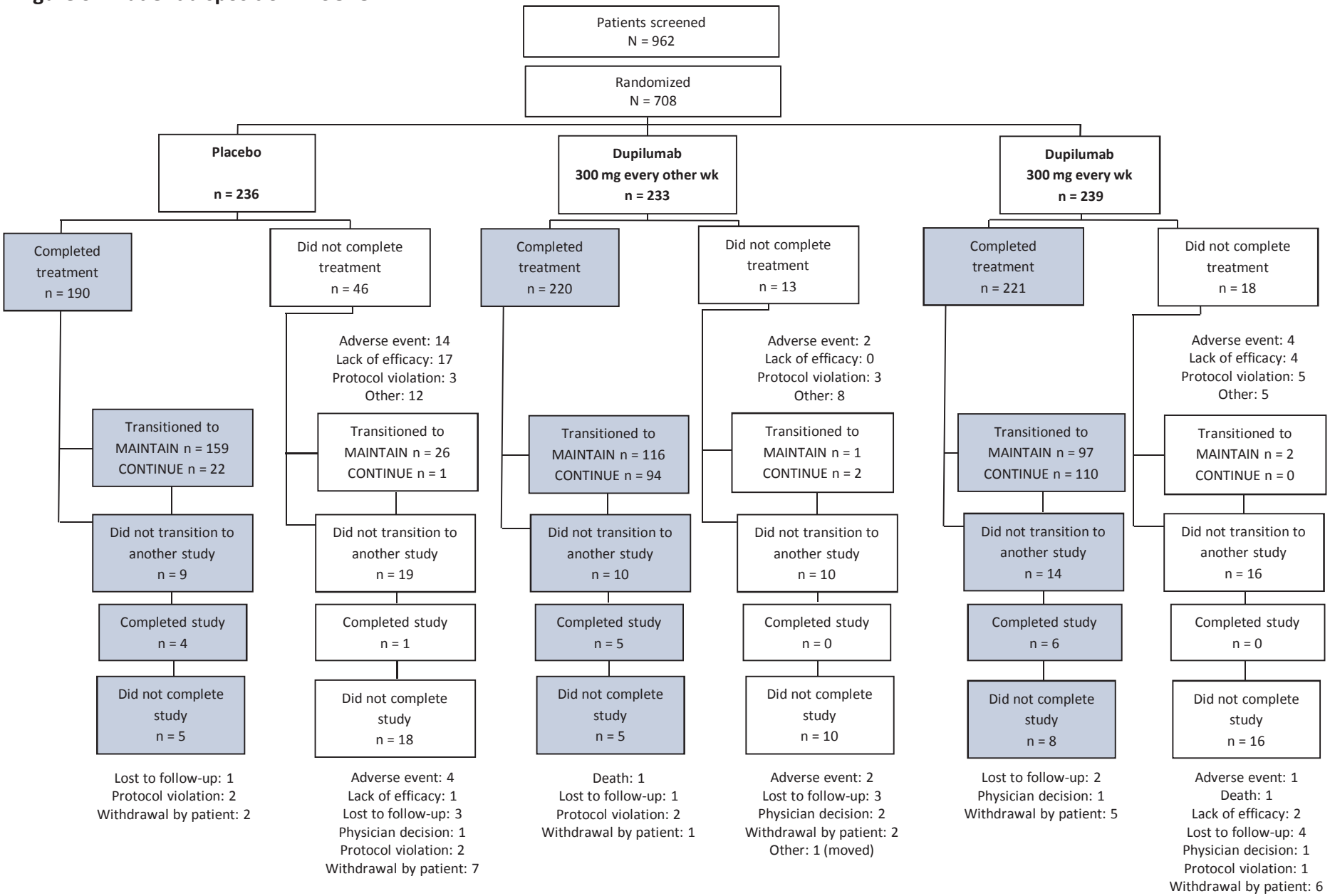
Supplemental figures

Figure S1. Patient disposition in SOLO 1



LIBERTY AD SOLO-CONTINUE, NCT02395133; LIBERTY AD MAINTAIN, NCT01949311.

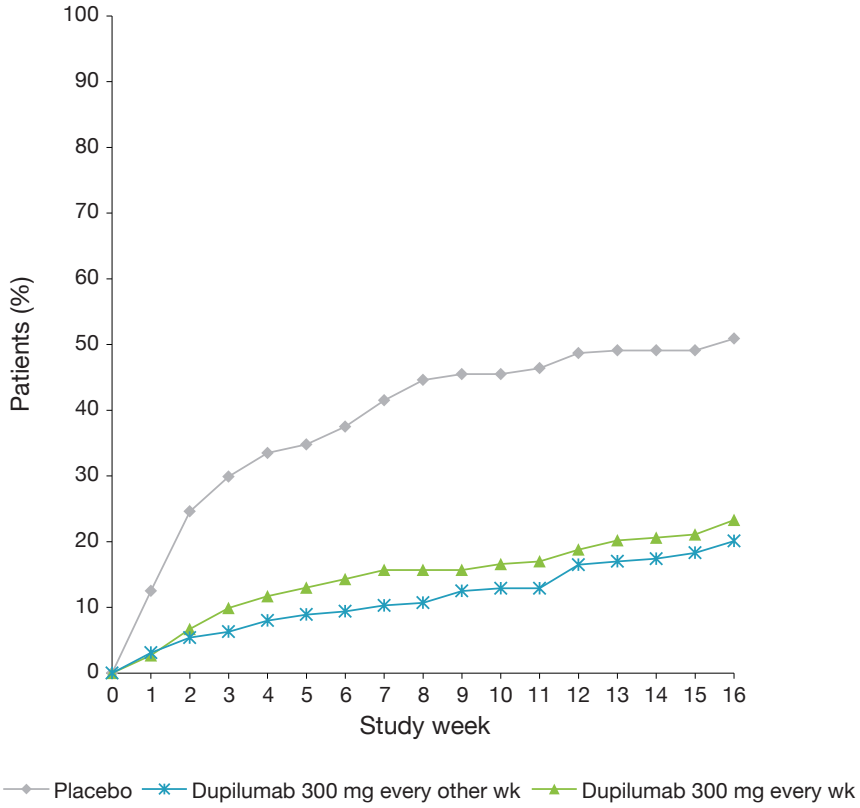
Figure S2. Patient disposition in SOLO 2



LIBERTY AD SOLO-CONTINUE, NCT02395133; LIBERTY AD MAINTAIN, NCT01949311.

Figure S3. Cumulative Proportion of Patients Receiving Rescue Therapy During the Treatment Period

A. SOLO 1



B. SOLO 2

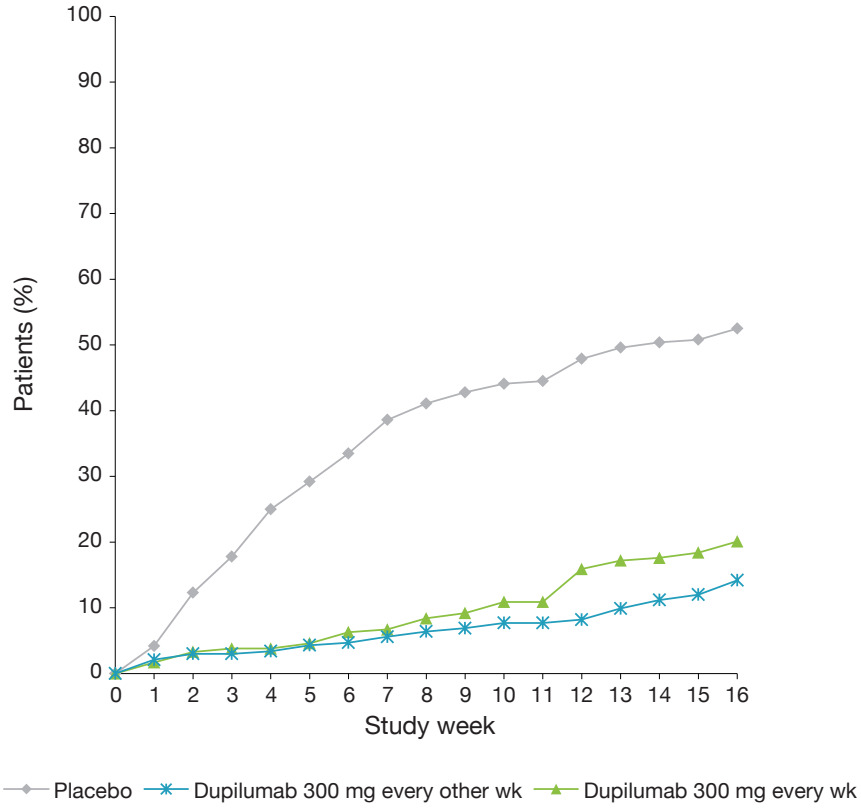
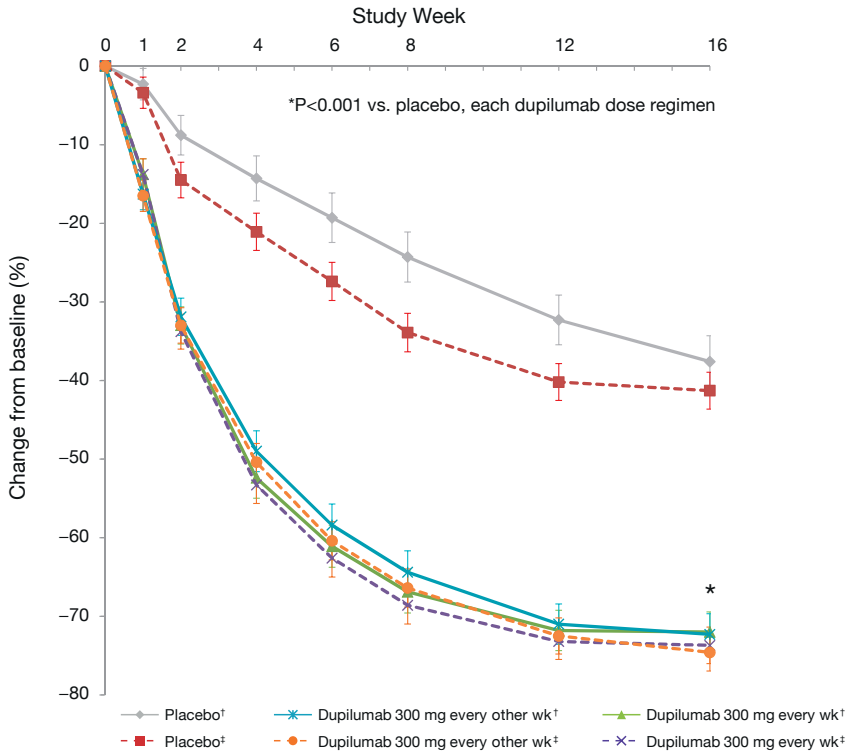
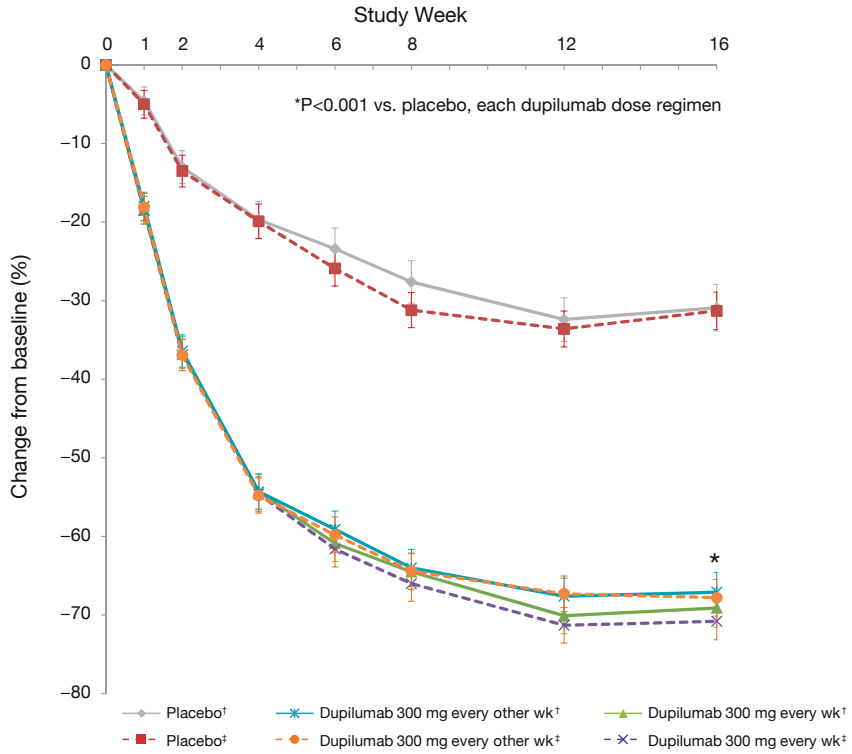


Figure S4. EASI: Least Squares Mean Percent Change Over Time, Primary Analysis, and Sensitivity Analysis

A. SOLO 1



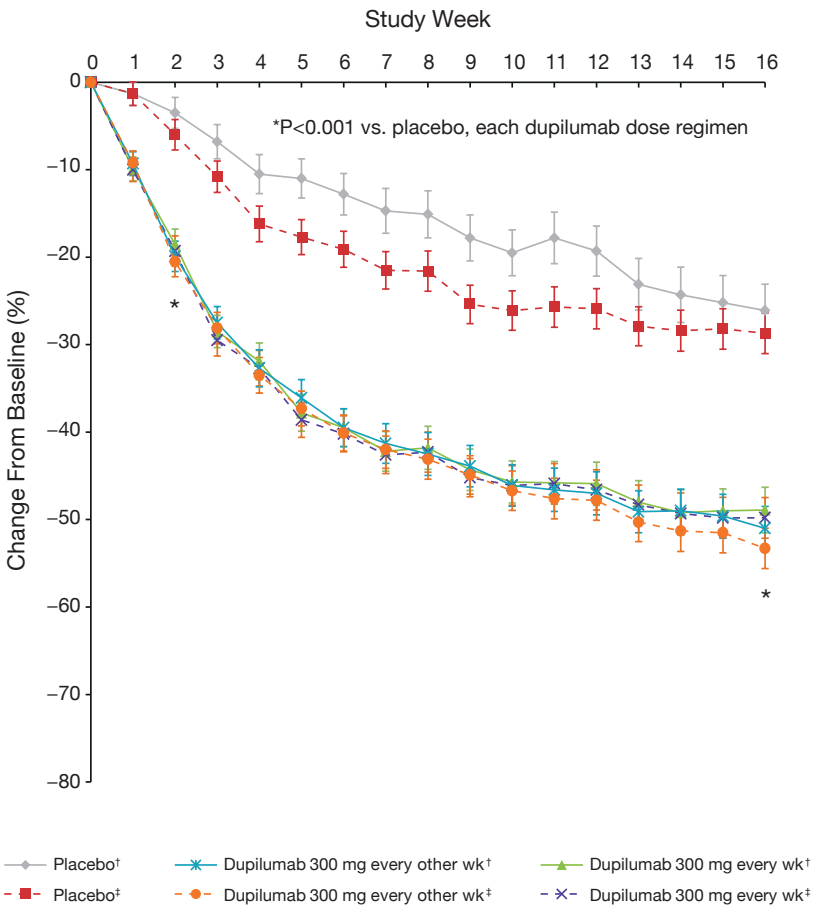
B. SOLO 2



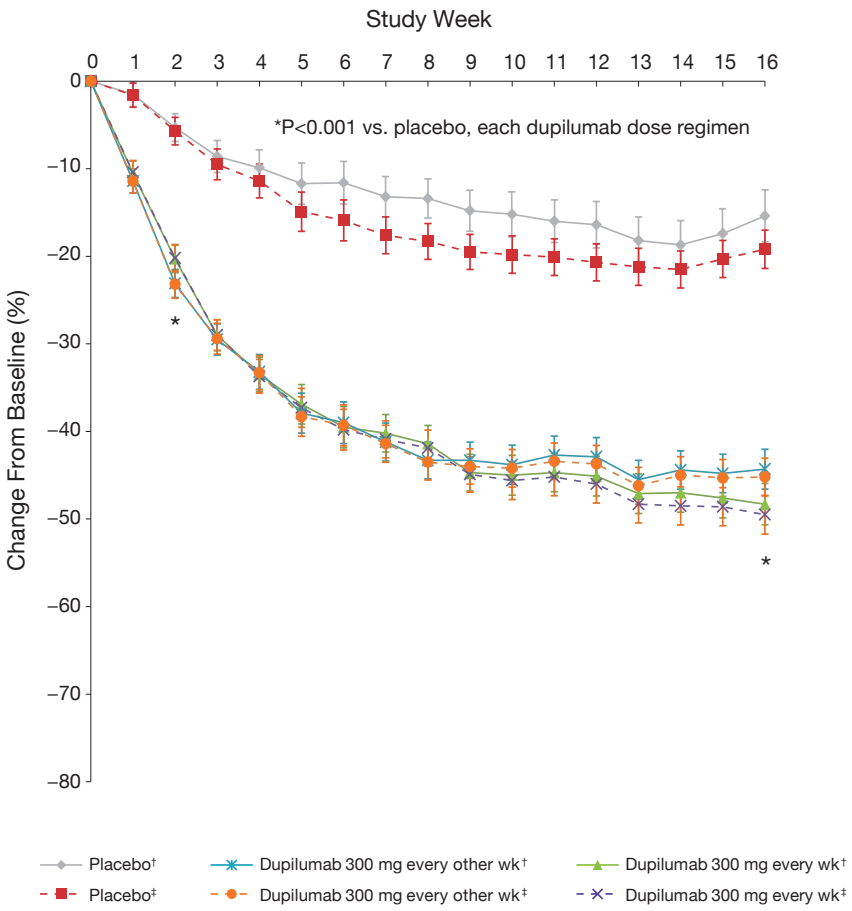
† Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.
EASI, Eczema Area and Severity Index.

Figure S5. Pruritus Numerical Rating Scale: Least Squares Mean Percent Change Over Time, Primary Analysis, and Sensitivity Analysis

A. SOLO 1



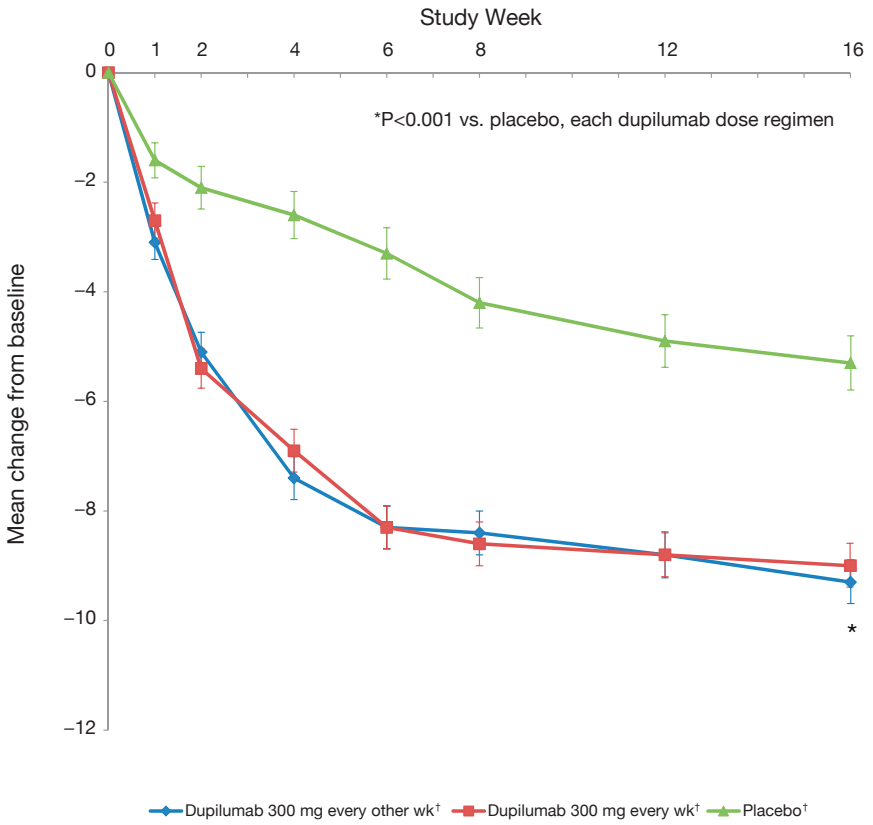
B. SOLO 2



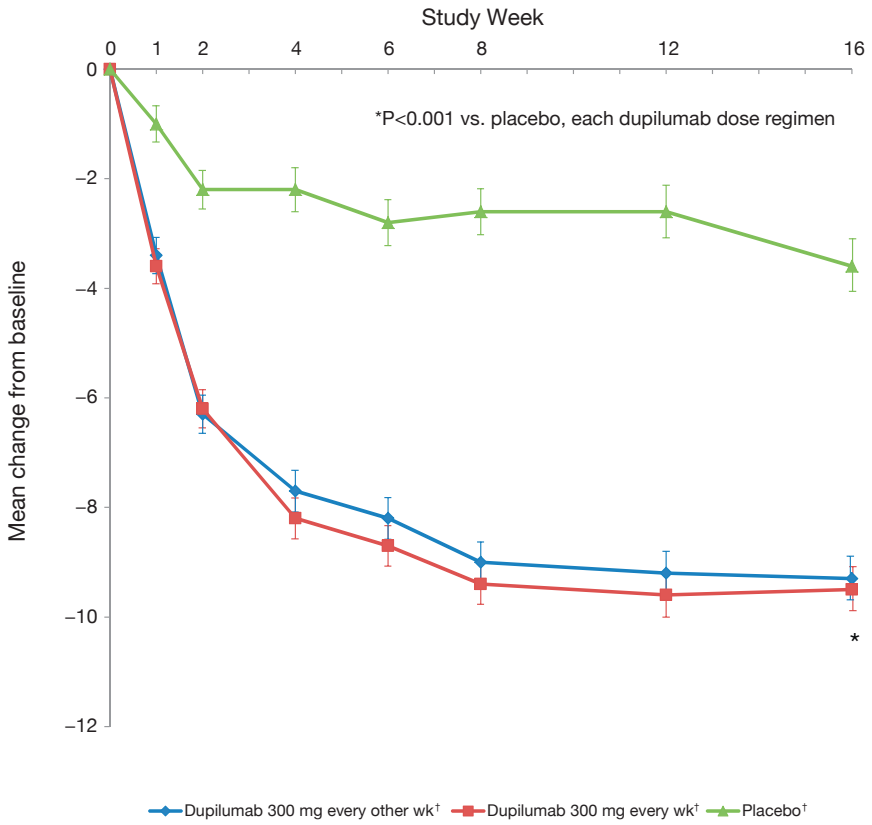
†Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.

Figure S6. Least Squares Mean Change From Baseline in DLQI in SOLO 1 and SOLO 2

A. SOLO 1



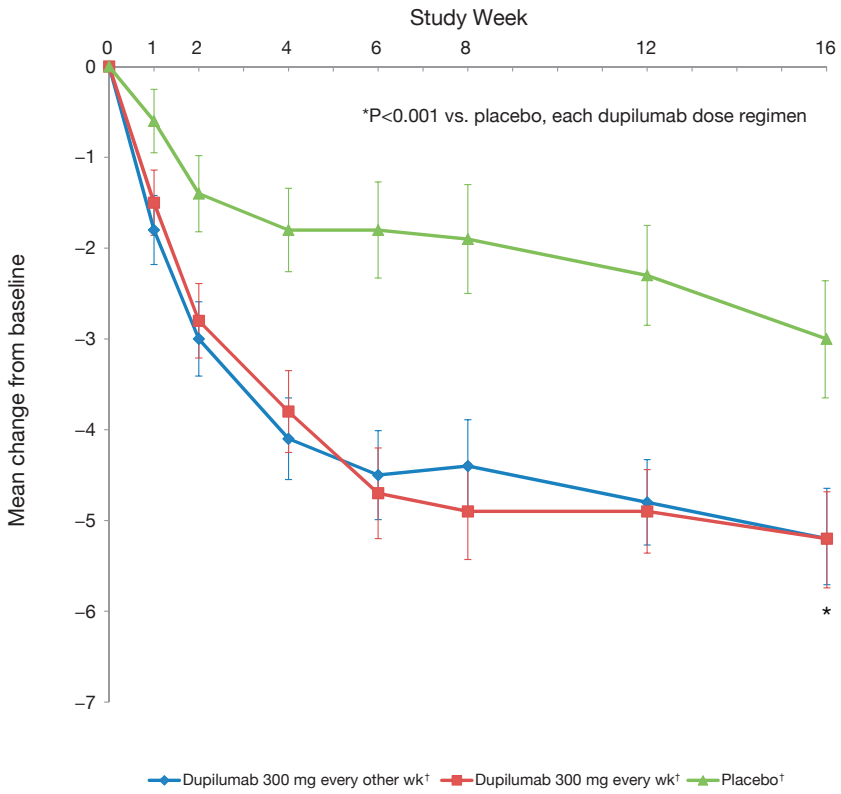
B. SOLO 2



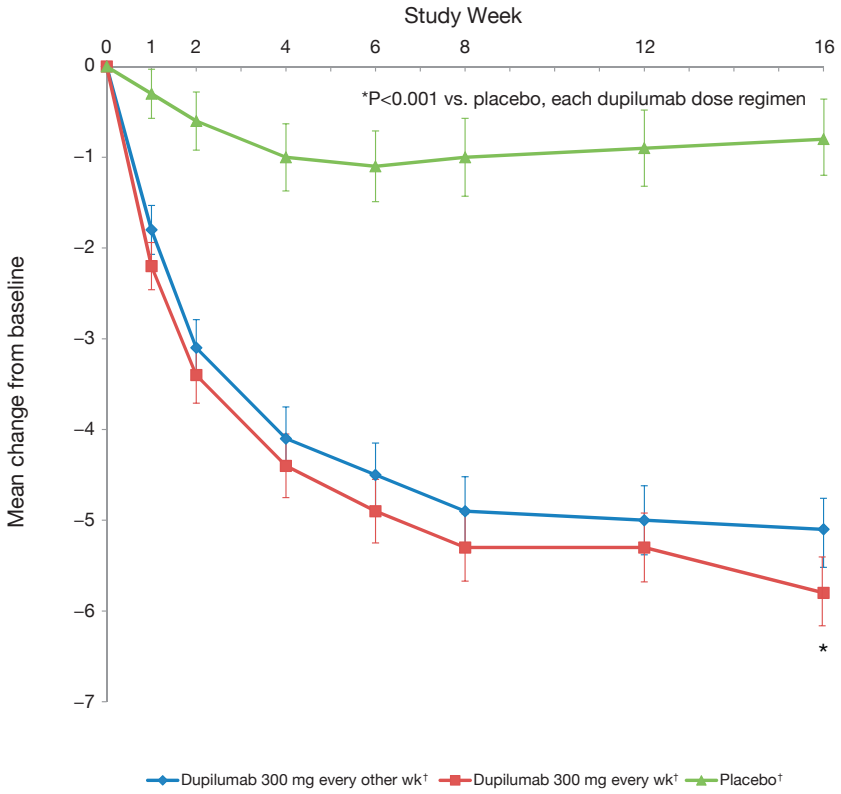
†Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.
DLQI, Dermatology Life Quality Index.

Figure S7. Least Squares Mean Change From Baseline in HADS Total Score in SOLO 1 and SOLO 2

A. SOLO 1



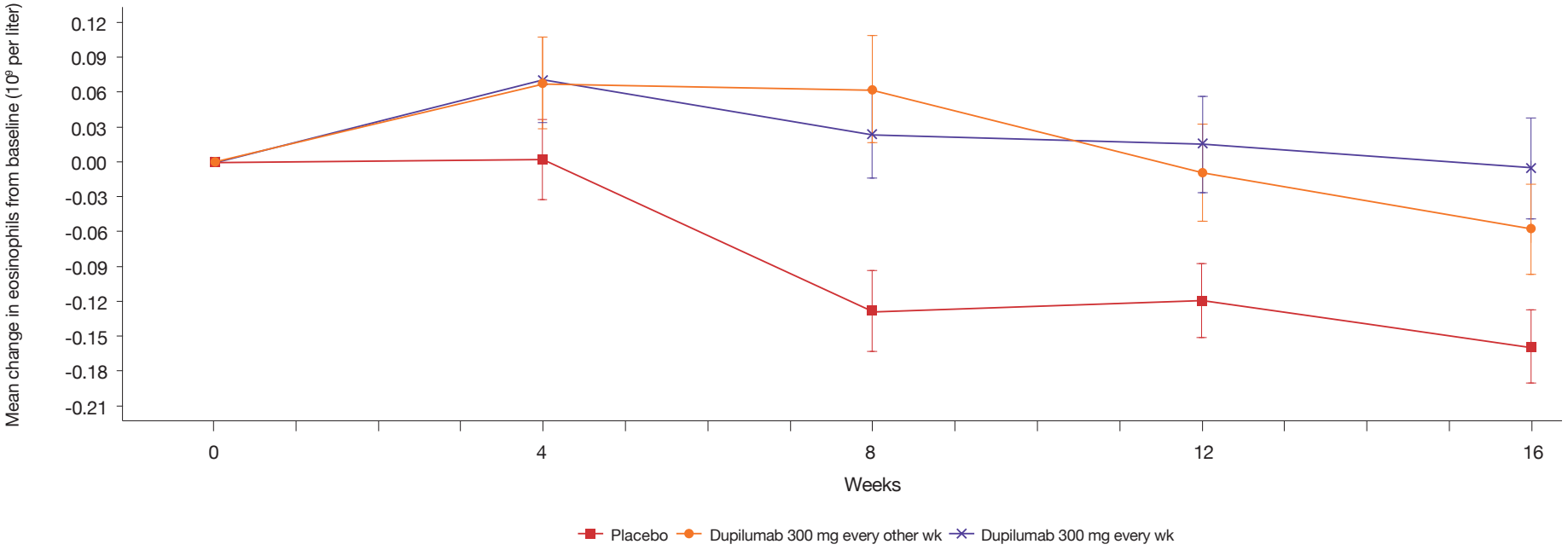
B. SOLO 2



†Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.
HADS, Hospital Anxiety and Depression Scale.

Figure S8. Change in Average Eosinophils (10^9 per Liter) From Baseline Through Week 16

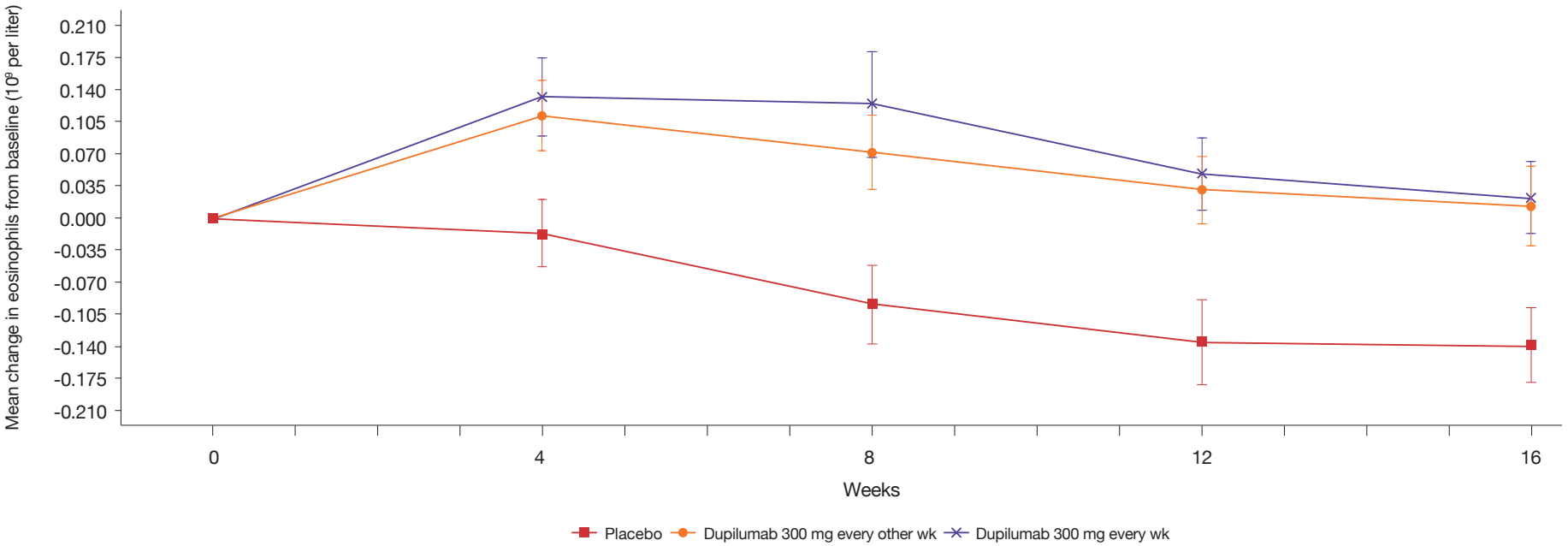
A. SOLO 1



Number of patients in each visit					
Dupilumab 300 mg qw (N=218)	216	207	200	195	199
Dupilumab 300 mg q2w (N=229)	229	217	215	212	216
Placebo qw (N=222)	221	204	194	191	197

Figure S8. Change in Average Eosinophils (10^9 per Liter) From Baseline Through Week 16

B. SOLO 2



Number of patients in each visit					
Dupilumab 300 mg qw (N=237)	237	222	216	218	214
Dupilumab 300 mg q2w (N=236)	236	220	216	219	218
Placebo qw (N=234)	233	222	208	207	214

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