Clinical Study Protocol

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY INVESTIGATING THE EFFICACY AND SAFETY OF MULTIPLE DUPILUMAB DOSE REGIMENS ADMINISTERED AS MONOTHERAPY FOR MAINTAINING TREATMENT RESPONSE IN PATIENTS WITH ATOPIC DERMATITIS

Compound:	Dupilumab
Clinical Phase:	3
Protocol Number:	R668-AD-1415
Protocol Version:	R668-AD-1415.03
Amendment 3 Date of Issue:	12 Oct 2016
Amendment 2 Date of Issue:	23 Feb 2016
Amendment 1 Date of Issue:	10 Feb 2015
Original Date of Issue:	11 Nov 2014
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[redacted]

AMENDMENT 3 (12 OCTOBER 2016)

The purpose of amendment 3 is to update and revise the protocol sections addressing study endpoints and statistical considerations, and to ensure concordance with the final Statistical Analysis Plan (SAP). The primary objective of the study is to assess the ability of different dupilumab dose regimens, administered as monotherapy, to maintain the treatment response achieved after 16 weeks of initial treatment. One of the current co-primary endpoints, IGA(0,1) has been helpful to assess initial treatment response but lacks adequate sensitivity to optimally characterize maintenance of response over time for different dosing regimens. As such, a more sensitive co-primary endpoint has been selected to better support the above study objective. The main changes are as follows:

- Downgrade Investigator's Global Assessment (IGA)(0,1) from co-primary to a key secondary endpoint. This endpoint cannot be analyzed in the entire randomized population (requires subset analysis in patients with IGA 0,1 at baseline), it does not adequately characterize dupilumab's clinical effect over time, and it lacks the sensitivity necessary to support the objective of the study, which is to differentiate between the treatment groups analyzed with respect to maintenance vs. loss of response
- Add a co-primary endpoint based on percent change in Eczema Area and Severity Index (EASI) score, which is analyzed in the entire randomized population (full analysis set [FAS]). This endpoint provides improved sensitivity to differentiate between maintenance vs. loss of response and better support for the study objective.
- Change the statistical testing methodology of multiplicity control, ie, from parallel testing of each of the 3 dose groups vs. placebo (with a 3-way alpha split and 0.0167 significance level) to hierarchical testing at a 0.05 significance level. In this hierarchical testing, co-primary and key secondary endpoints are tested first for the high dose group; if significant, the testing sequence will move down to the next lower dose group. Sequential testing, in the descending order of dupilumab dose regimens, is consistent with the expected dose-response relationships, and provides higher power to detect differences in the tested endpoints under monotone dose-response assumptions.

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

Change	Section Changed
Revise and re-organize endpoints	Synopsis, Endpoints Section 8.2 Primary and Secondary Endpoints
Revise the statistical considerations section and related sections	Synopsis, Population: Sample Size; Statistical Plan: Sample Size, Efficacy Analysis Set, Methods Section 4.1 Number of Patients Planned Section 5.5 Method of Treatment Assignment Section 9.1 Statistical Hypothesis Section 9.2 Justification of Sample Size Section 9.3 Analysis Sets Section 9.4 Statistical Methods
Additional minor corrections and clarifications	Section 9.3.3 Other Analysis Sets

AMENDMENT 2 (23 FEBRUARY 2016)

The purposes of amendment 2 are to:

- Clarify that patients who complete the end of treatment visit in SOLO-1 (R668-AD-1334) and SOLO-2, (R668-AD-1416) and who fulfill eligibility criteria, will be enrolled in the current study
- Further clarify the definition of adequate birth control for sexually active women of reproductive potential in the "Exclusion Criteria"
- Provide more specific guidance on escalation of rescue treatment
- Update information regarding infections requiring systemic treatment under "Reasons for Temporary Discontinuation of Study Drug" to improve clarity and accuracy, as oral treatment is also a systemic route of administration
- Add an additional restriction to "Prohibited Medications and Procedures" to include all atopic dermatitis (AD) treatments, including off-label treatments, with the exception of those specifically allowed in the protocol
- Remove ACQ-5 and SNOT-22 questionnaires from the study visit descriptions of visit 4 and visit 7 to align with the schedule of events
- Correct study drug administration up through week 35, instead of week 36
- Change the anti-drug antibody (ADA) variables and text throughout the protocol to distinguish between transient and persistent ADA responses.

- Make changes throughout the protocol to the follow-up of patients with positive ADA titer at their last study visit to ensure that patients with ADA positive titer are not lost to follow-up.
- Provide text to clarify the relationship between rescue medications and prohibited medications
- Increase the clarity and accuracy of the conditions for the early termination visit
- Add footnotes to the bilirubin and creatine phosphokinase (CPK) laboratory tests to be consistent with the phase 3 protocols
- Add additional text in Laboratory Testing "Other Laboratory Tests" for improved clarity
- Clarify that the sample size is an estimate, based on the anticipated number of eligible patients enrolled from the SOLO-1 (R668-AD-1334) and SOLO-2 (R668-AD-1416) clinical trials, and not based on a predefined quota
- Added sub-sections in the Statistical Plan to clarify the definitions of Pharmacokinetic (PK) and Anti-drug Antibody (ADA) analysis sets
- Make editorial changes for correction, clarity, and/or consistency

AMENDMENT 1 (10 FEB 2015)

The purposes of amendment 1 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," and to add Japan to the countries that will use the co-primary endpoints
- Change "other endpoints" to "other secondary endpoints" for clarity and consistency with the terminology used in the parent studies (R668-AD-1334 and -1416)
- Move the endpoint "change in SCORing Atopic Dermatitis (SCORAD) from baseline to week 36" from key secondary endpoints section to the "other secondary endpoints" section, and revise the endpoint from "change … from baseline …" to "percent change … from baseline …"
- Add per protocol set (PPS) for efficacy analysis
- Clarify the description, using language consistent with that used in the parent studies (R668-AD-1334 and -1416), 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; add description of the mixed-effect model with repeated measures (MMRM) method (which will account

for the missing data) to be used for continuous secondary endpoints in EU, EU reference market countries, and Japan.

- Remove the last paragraph in the emergency unblinding section regarding unblinding of designated study pharmacist/designee at the study site
- Revise footnote 12 of Table 1 to clarify that noninvasive skin swabs may be (instead of "to be" as previously stated) conducted at selected sites only
- Add study drug accountability in the schedule of events tables
- Add a label "primary endpoint visit" for visit 10/week 36/day 252 (+/- 3 days) for clarity
- Add an instruction regarding fasting before blood sample collection
- For exploratory biomarker testing: change the phrase from "… samples will be collected and banked" to "… samples will be collected and may be banked"
- Make editorial changes for correction, clarity and/or consistency

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of Multiple Dupilumab Dose Regimens Administered as Monotherapy for Maintaining Treatment Response in Patients with Atopic Dermatitis
Site Locations	Global
Principal Investigator	Not applicable
Objectives	The primary objective of the study is to assess the ability of different dupilumab dose regimens, administered as monotherapy, to maintain the treatment response achieved after 16 weeks of initial treatment with dupilumab monotherapy compared to placebo. The secondary objective of the study is to assess the safety of different dupilumab doses regimens administered as monotherapy over a period of 36 weeks.
Study Design	This is a phase 3, randomized, double-blind, placebo-controlled study to determine the ability of different dupilumab dose regimens to maintain the treatment response achieved by patients with atopic dermatitis (AD) after an initial 16-week treatment with dupilumab monotherapy in 1 of 2 initial treatment studies (R668-AD-1334 or R668-AD-1416). To be eligible for this maintenance study, all patients must have achieved an Investigator's Global Assessment (IGA) 0 or 1 or Eczema Area and Severity Index (EASI)-75 at week 16 in either initial treatment study after treatment with 300 mg weekly (qw) subcutaneous (SC) or 300 mg every 2 weeks (q2w) SC. Patients will be randomized 2:1:1:1 to 1 of the following 2 treatment arms, depending on the dose of dupilumab received in the initial treatment study (300 mg qw SC or 300 mg q2w SC): • Patients who received 300 mg qw SC in the initial treatment studies will be randomized 2:1:1:1 to receive 1 of the following 4 treatment regimens: – Dupilumab 300 mg qw SC – Dupilumab 300 mg every 4 weeks (q4w) SC – Dupilumab 300 mg every 8 weeks (q8w) SC – Placebo • Patients who received 300 mg q2w SC in the initial treatment studies will be randomized 2:1:1:1 to receive 1 of the following

4 treatment regimens:

- Dupilumab 300 mg q2w SC
- Dupilumab 300 mg q4w SC
- Dupilumab 300 mg q8w SC
- Placebo

Randomization will be further stratified according to region (North America, Europe, Asia, and Japan) and baseline IGA scores (IGA=0 vs. IGA=1 vs. IGA>1).

The study consists of a 36-week treatment period and a 12-week follow-up period.

Following randomization on day 1 (which is week 16 in the initial treatment studies), patients will begin study treatment. Patients will return to the clinic every 4 weeks (at weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36). Patients will continue to receive study drug (dupilumab or placebo) weekly for 36 weeks. Patients randomized to q2w, q4w, and q8w regimens will receive placebo during weeks when dupilumab is not administered.

Patients who complete the 36-week treatment period may enroll in an open-label extension study starting at week 36. Patients who do not transition into the open-label extension study before week 48 will undergo an additional follow-up visit at week 40 and a final (end of study) visit at week 48.

For the purpose of maintaining the blind of the treatment in the initial treatment studies, placebo responders (defined as patients who received placebo and who achieved an IGA=0 or 1 or EASI-75 at week 16 in the initial treatment studies) will also be eligible to enroll in the current study, but they will not be randomized; these placebo responder patients will receive placebo during the entire 36-week treatment period in this study, but will constitute a separate treatment group and will not be included in any efficacy analysis set for this maintenance study.

If medically necessary (eg, to control intolerable AD symptoms), patients may receive rescue treatment for AD symptoms. Whenever possible, the first rescue step should consist of medium potency topical corticosteroids (TCS) following a standardized regimen. As part of this standardized regimen, low potency TCS or topical calcineurin inhibitors (TCI) may be used on limited "problem areas" (eg, face, intertriginous, genital areas) that cannot be safely treated with medium potency TCS, as deemed necessary by the investigator.

Rescue treatment can be escalated if patients do not respond adequately to this initial approach within 7 days. If disease severity or other medical considerations do not permit this gradual rescue approach, patients may be rescued directly with higher potency topical medications or with systemic

	treatments. Before initiating or escalating rescue treatment, patients should be evaluated in the clinic, when all efficacy parameters should be assessed. An unscheduled visit may be used for this purpose, if necessary. For the purpose of analyzing the primary and key secondary efficacy endpoints, patients who receive rescue treatment during the study treatment period will be considered study treatment failures, but they may continue study treatment if rescue consists of topical treatments. Patients who receive rescue treatment with systemic corticosteroids or other systemic nonsteroidal immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) will be temporarily discontinued from study drug. Study treatment may be resumed after rescue treatment is completed, if and when deemed appropriate by the medical monitor and the investigator, but not sooner than 5 half-lives after the last dose of systemic rescue medication has been administered. All patients will continue with the schedule of study visits and assessments, regardless of rescue treatment or completion of study treatment.
Study Duration	Each patient's participation in the study will be up to approximately 48 weeks.
Population	
Sample Size:	Approximately 420 dupilumab-treated patients from approximately 300 global sites that participated in the initial studies will be enrolled. This number is an estimation that is based on results from phase 2 studies and does not represent a quota or a cap. All patients who complete the end of treatment visit (week 16 visit) in the SOLO-1 (R668-AD-1334) or SOLO-2 (R668-AD-1416) studies, and who fulfill the eligibility criteria, will be enrolled in the current study.
Target Population:	The study population consists of adults with moderate-to-severe AD who have participated in either of the 2 initial treatment studies (R668-AD-1334 or R668-AD-1416) and who have achieved either of the 2 treatment success criteria: IGA = 0 or 1 (clear or almost clear) at week 16, or EASI-75 (at least 75% reduction in EASI score from baseline to week 16).
Treatments	
Study Drug	Dupilumab SC
Dose/Route/Schedule:	300 mg qw, 300 mg q2w, 300 mg q4w, or 300 mg q8w administered SC from day 1 to week 36
Placebo	Matching placebo SC injection
Route/Schedule:	Patients will receive placebo during weeks when dupilumab is not administered.

Background Treatment Dose/Route/Schedule:	Patients are required to continue applying moisturizers (emollients) that were initiated before day 1, at least twice daily throughout the study (all 48 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.
Endpoints	
Co-Primary:	• Difference between current study baseline and week 36 in percent change in EASI from the baseline of the initial treatment study (R668-AD-1334 or R668-AD-1416) • Percent of patients maintaining EASI-75 at week 36 in the subset of patients with EASI-75 at baseline
Key Secondary Endpoints:	• Percent of patients with an increase of ≥2 points in IGA from baseline to week 36, in the subset of patients with IGA (0,1) at baseline • Percent of patients with IGA(0,1) at week 36 in the subset of patients with IGA(0,1) at baseline • Percent of patients whose peak Pruritus NRS increased by 3 or more points from baseline to week 36 in the subset of patients with peak Pruritus NRS ≤7 at baseline
Procedures and Assessments	A variety of parameters will be collected during the study to assess the efficacy of dupilumab, including objective 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 treatment-emergent adverse events (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 levels at predetermined time points. Research samples and samples for exploratory biomarker analysis will be collected.
Statistical Plan	**Sample Size and Power:** Based on the number of eligible patients from the initial treatment studies (R668-AD-1334 and R668-AD-1416), approximately 420 patients will be included in the analysis. Assumptions used to calculate power for the

co-primary endpoints regarding the comparisons between dupilumab 300 mg qw or dupilumab 300 mg q2w and placebo were informed by data from completed dupilumab studies. They are as follows:

- Test (T) 1: Mean difference (baseline to week 36) in % change in EASI from the baseline EASI in the initial treatment study
  - Dupilumab ((300 mg qw or 300 mg q2w): 5%
  - Placebo: 35%
- T2: Percent of patients with EASI-75 at week 36
  - Dupilumab (300 mg qw or 300 mg q2w): 85%
  - Placebo: 30%

It is estimated that with the current sample size, 170 patients in the dupilumab 300 mg qw or q2w group, and 84 patients in the placebo group from each of the initial treatment dosing, the study will provide 99% power at the 2-sided 5% significance level to detect the expected differences between dupilumab and placebo for the co-primary endpoints.

Efficacy Analysis Set:

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

The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. A major protocol violation is one that may affect the interpretation of study results. 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 following information: 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: Treatment differences between dupilumab and placebo will be tested sequentially in a prespecified (descending) order for each of the co-primary and key secondary endpoints:

- T1: Mean difference (baseline to week 36) in % change EASI
- T2: Percent of patients with EASI-75 at week 36
- T3: Percent of patients with an increase of ≥ 2 points in IGA from baseline to week 36, in the subset of patients with IGA (0,1) at baseline
- T4: Percent of patients with IGA=0 or 1 at week 36 for patients with IGA=0 or 1 at baseline
- T5: Percent of patients with peak Pruritus NRS increased by ≥3 points from baseline to week 36

If an endpoint is significant at a 2-sided 0.05 level, the sequential analysis will continue for the next endpoint until the significance level is no longer met.

If all tests are significant from the primary to key secondary endpoints, the same hierarchical testing procedure will apply to dupilumab 300 mg q4w vs. placebo and then dupilumab 300 mg q8w vs. placebo. The testing order will be as follows:

1. High dose group (300 mg qw or q2w) vs placebo: in the order of T1, T2, T3, T4, then T5; then
2. Middle dose group (300 mg q4w) vs placebo: in the order of T1, T2, T3, T4, then T5; then
3. Low dose group (300 mg q8w) vs placebo: in the order of T1, T2, T3, T4, then T5

To account for the impact of rescue medication on efficacy:

- For binary response endpoints, a patient who received any rescue medication will be specified as a nonresponder from the time the rescue medication is used.
- For continuous endpoints, data after rescue treatment will be set to missing.
- If a patient withdraws from the study, this patient will be counted as a nonresponder for binary endpoints after withdrawal.

Continuous variable endpoints will be analyzed by using the multiple imputation (MI) with analysis of covariance (ANCOVA) model. Graphs of least-square (LS) means ±SE by visit for change from baseline related variables will be presented.

Missing data will be imputed using the MI with ANCOVA model for the primary analysis. Patients' efficacy data through week 36 after the rescue medication usage will be set to missing first, and then be imputed by the MI method.

For binary endpoints, the Cochran-Mantel-Haenszel test adjusted by randomization strata (disease severity: baseline IGA=0 vs IGA=1 vs IGA>1, and region: Americas, Europe, and Asia Pacific including Japan) will be used. If a patient receives rescue medication or withdraws from the study, that patient will be considered as a nonresponder.

For time-to-event endpoints, the log rank test stratified by the randomization strata will be used. The Kaplan-Meier curve will be provided.

Safety Analysis: Will be based on the safety analysis set (SAF), which includes all randomized patients who received any amount of study drug and is based on the treatment received (as treated). If a patient receives a dose regimen other than the assigned dose regimen, that patient will be considered as treated with the lowest active dose regimen. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACQ-5	Asthma Control Questionnaire
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of covariance
Anti-dsDNA	Anti-double-stranded DNA
Anti-TPO	Anti-thyroid peroxidase antibody
ARGUS	Pharmacovigilance and clinical safety software system
AST	Aspartate Aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EQ VAS	EQ visual analogue scale
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
hs-CRP	High sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E

IL	Interleukin
IL-4Rα	Iterleukin-4 receptor alpha subunit
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
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
q8w	Every 8 weeks
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SNOT-22	Sinonasal Outcome Test
SOC	System organ class
T	Test
TARC	Thymus and activation-regulated chemokine (CCL17)
TEAE	Treatment-emergent adverse event
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Th1	Type 1 helper T cell
Th2	Type 2 helper T cell
ULN	Upper limit of normal

VAS	Visual Analogue Scale
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus, dry skin, and eczematous lesions. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be associated with significant disability 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 15% to 30% of children and 2% to 10% of adults are affected by AD (Bieber 2008).

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 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. 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, 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, 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. Antihistamines, which are primarily sedating, are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited. 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 α (infliximab, etanercept), anti-immunoglobulin E (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 who are intolerant of, or whose AD is not adequately controlled with, topical treatments. This population includes patients who are often treated with systemic corticosteroids, as well as other nonselective immunosuppressants, including cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, 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.

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 study to determine the ability of different dupilumab dose regimens, administered as monotherapy, to maintain treatment response achieved after an initial 16-week treatment with dupilumab monotherapy in patients with moderate-to-severe AD, inadequately controlled with topical medications.

Patients enrolled in this study are those who achieved treatment success criteria (Investigator's Global Assessment [IGA] 0 or 1 or Eczema Area and Severity Index [EASI]-75) after receiving dupilumab (300 mg weekly [qw] or 300 mg every 2 weeks [q2w]) for 16 weeks in 2 initial treatment studies (R668-AD-1334 or R668-AD-1416). The purpose of the study is to determine the ability of different dupilumab dose and frequency regimens to maintain treatment response over a period of 36 weeks.

The study is designed as a randomized dose frequency reduction/dose withdrawal clinical investigation. Eligible patients will be randomized to either continue the same dose regimen received in the initial treatment study (300 mg qw or 300 mg q2w), to step down to lower dose frequency regimens (300 mg every 4 weeks [q4w] or 300 mg every 8 weeks [q8w]), or to discontinue dupilumab and receive placebo during the current study.

To maintain the blinding of the initial treatment studies, patients who received placebo and achieved treatment success criteria (IGA 0 or 1 or EASI-75) in these studies will also be enrolled

in the current study, but they will not be randomized; these patients will constitute a separate cohort and will continue to receive placebo during the entire 36-week study treatment period.

1.2.2. Rationale for Dose Selection

Doses selected for this study reflect the study objectives and the study design. The higher dose frequency groups (300 mg qw and 300 mg q2w) serve to determine the degree of maintenance of response in patients who continue the dose regimen in the initial treatment study. The 2 lower dose frequency dupilumab dose groups (300 mg q4w and 300 mg q8w) represent step decreases in dosing frequency. This ranging is typical for dose finding studies. Finally, the placebo group will serve as the control, assuming that patients who discontinue dupilumab will largely lose treatment response. For analysis purposes, each active treatment group will be compared to placebo.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the ability of different dupilumab dose regimens, administered as monotherapy, to maintain the treatment response achieved after 16 weeks of initial treatment with dupilumab monotherapy compared to placebo.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety of different dupilumab dose regimens administered as monotherapy over a period of 36 weeks.

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 3, randomized, double-blind, placebo-controlled study to determine the ability of different dupilumab dose regimens to maintain the treatment response achieved by patients with AD after an initial 16-week treatment with dupilumab monotherapy in 1 of 2 initial treatment studies (R668-AD-1334 or R668-AD-1416).

To be eligible for this maintenance study, all patients must have achieved an IGA 0 or 1 or EASI-75 at week 16 in either initial treatment study after treatment with 300 mg qw subcutaneous (SC) or 300 mg q2w SC.

Patients will be randomized 2:1:1:1 to 1 of the following 2 treatment arms, depending on the dose of dupilumab received in the initial treatment study (300 mg qw SC or 300 mg q2w SC):

- Patients who received 300 mg qw SC in the initial treatment studies will be randomized 2:1:1:1 to receive 1 of the following 4 treatment regimens:
  - Dupilumab 300 mg qw SC
  - Dupilumab 300 mg q4w SC
  - Dupilumab 300 mg q8w SC
  - Placebo
- Patients who received 300 mg q2w SC in the initial treatment studies will be randomized 2:1:1:1 to receive 1 of the following 4 treatment regimens:
  - Dupilumab 300 mg q2w SC
  - Dupilumab 300 mg q4w SC
  - Dupilumab 300 mg q8w SC
  - Placebo

Randomization will be further stratified according to region (North America, Europe, Asia, and Japan) and baseline IGA scores (IGA=0 vs. IGA=1 vs. IGA >1).

The study consists of a 36-week treatment period and a 12-week follow-up period.

Following randomization on day 1 (which is week 16 in the initial treatment studies), patients will begin study treatment. Patients will return to the clinic every 4 weeks (at weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36). Patients will continue to receive study drug (dupilumab or placebo) weekly for 36 weeks. Patients randomized to q2w, q4w, and q8w regimens will receive placebo during weeks when dupilumab is not administered. A study flow diagram is in Figure 1.

Patients who complete the 36-week treatment period may enroll in an open-label extension study starting at week 36. Patients who do not transition into the open-label extension study before week 48 will undergo an additional follow-up visit at week 40 and a final (end of study) visit at week 48.

For the purpose of maintaining the blind of the treatment in the initial treatment studies, placebo responders (defined as patients who received placebo and who achieved an IGA 0 or 1 or EASI-75 at week 16 in the initial treatment studies) will also be eligible to enroll in the current study, but they will not be randomized; these placebo responder patients will receive placebo during the entire 36-week treatment period in this study, but will constitute a separate treatment group and will not be included in any efficacy analysis set for this maintenance study.

If medically necessary (eg, to control intolerable AD symptoms), patients may receive rescue treatment for AD symptoms (see Section 5.3 for details).

Figure 1: Study Flow Diagram

Treatment Period (Study Weeks, Days)				Follow-Up	
V1	V2	V3-V10 (q4w)		V11	V12
Baseline					End of Study
(Day 1*)	W4 (Day 29)	W8-W32 (Day 57-Day 225)	W36** (Day 253)	W40 (Day 281)	W48 (Day 337)

*Week 16 in the initial treatment studies – R668-AD-1334 or R668-AD-1416

**Patients will receive weekly study drug (dupilumab and/or placebo, depending on their treatment arm) for 36 weeks

3.2. Planned Interim Analysis

No interim analysis is planned.

3.3. Study Committees

3.3.1. Independent Data Monitoring

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

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

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

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Approximately 420 dupilumab-treated patients from approximately 300 global sites that participated in the initial studies will be enrolled. This number is an estimation that is based on results from phase 2 studies and does not represent a quota or a cap. All patients who complete the end of treatment visit (week 16 visit) in the SOLO-1 (R668-AD-1334) or SOLO-2 (R668-AD-1416) studies, and who fulfill the eligibility criteria, will be enrolled in the current study.

4.2. Study Population

The study population consists of adults with moderate-to-severe AD who have participated in either of the 2 initial treatment studies and achieved the treatment success criteria, as noted below.

4.2.1. Inclusion Criteria

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

1. Must have completed the treatment phase in 1 of the two 16-week initial treatment studies (R668-AD-1334 or R668-AD-1416).
2. Must have achieved at least 1 of the following 2 treatment success criteria:

   IGA = 0 or 1 (clear or almost clear) at week 16

   OR

   EASI-75 (at least 75% reduction in EASI score from baseline to week 16)
3. Must be willing and able to comply with clinic visits and study-related procedures
4. Must provide signed informed consent
5. Must be able to understand and complete study-related questionnaires

4.2.2. Exclusion Criteria

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

1. Receipt of rescue medication for AD in the initial treatment study
2. Any conditions that require permanent discontinuation of study treatment in either initial treatment study
3. Planned or anticipated major surgical procedure during the patient's participation in this study
4. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during this study
5. 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, whenever engaging in heterosexual intercourse, 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 (eg, 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 render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who withdraw prematurely from the study will be asked to complete study assessments, as described in Section 6.2.2.

4.4. Replacement of Patients

Patients prematurely discontinued from study drug will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

Dupilumab 150 mg/mL: Each 2.25 mL single-use, prefilled glass syringe with snap-off cap delivers 2.0 mL (150 mg/mL) or 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 be randomized 2:1:1:1 to 1 of the following 2 treatment arms, depending on the dose of dupilumab received in the initial treatment study:

- Patients who received 300 mg qw SC in the initial treatment study will be randomized 2:1:1:1 to receive:
  - Dupilumab 300 mg qw SC
  - Dupilumab 300 mg q4w SC
  - Dupilumab 300 mg q8w SC
  - Placebo
- Patients who received 300 mg q2w SC in the initial treatment study will be randomized 2:1:1:1 to receive:
  - Dupilumab 300 mg q2w SC
  - Dupilumab 300 mg q4w SC
  - Dupilumab 300 mg q8w SC
  - Placebo

At each study visit through week 32, patients will be provided with a 4-week supply of study drug (dupilumab and/or placebo, depending on their treatment arm) for self-administration, or for administration by a caregiver outside the clinic. Patients who prefer to have the clinic staff administer study drug may choose to have injections administered in the clinic.

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, study drug should be administered only into areas of normal-looking skin. Instructions for recording and reporting injection site reactions will be provided in the study reference manual.

Instructions on dose preparation are provided in the pharmacy manual.

5.2. Background Treatments

All patients are required to continue to apply moisturizers (emollients) at least twice daily throughout the study (all 48 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. Although patients may not initiate treatment with prescription moisturizers or moisturizers containing additives (urea, ceramides, etc.) during the study, patients may continue using stable doses of such moisturizers if initiated before day 1.

5.3. Rescue Treatments

If medically necessary (eg, to control intolerable AD symptoms), rescue treatment for AD with otherwise prohibited medications (see Section 5.7.1) may be provided to study patients, at the discretion of the investigator. Whenever possible, the first rescue step should consist of medium potency TCS following a standardized regimen. As part of this standardized regimen, low potency TCS or TCI may be used on limited "problem areas" (eg, face, intertriginous, genital areas) that cannot be safely treated with medium potency TCS, as deemed necessary by the investigator.

Rescue treatment can be escalated if patients do not respond adequately to this initial approach within 7 days. If disease severity or other medical considerations do not permit this gradual rescue approach, patients may be rescued directly with higher potency topical medications or with systemic treatments. **NOTE: Systemic rescue treatments may necessitate temporary discontinuation of study drug (see next paragraph).** Before initiating or escalating rescue treatment, patients should be evaluated in the clinic, when all efficacy parameters should be assessed. An unscheduled visit may be used for this purpose, if necessary.

For the purpose of analyzing the primary and key secondary efficacy endpoints, patients who receive rescue treatment during the study treatment period will be considered study treatment failures, but they may continue study treatment if rescue consists of topical treatments. Patients who receive rescue treatment with systemic corticosteroids or systemic nonsteroidal immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) will be temporarily discontinued from study drug. 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 has been administered. All patients will be asked to complete study assessments per the schedule of events (Table 1), whether or not they completed study treatment or received rescue treatment.

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 to complete all study assessments per the visit schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per Section 6.2.2.

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
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Pregnancy
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immunocompromised 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 diagnosis of 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 permanent discontinuation of study treatment include:

- Treatment with prohibited concomitant medication or procedure under certain circumstances (see Section 5.7.1)

5.4.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- Clinically important laboratory abnormalities, such as:
  - 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) >10 x ULN
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents for longer than 2 weeks
- Treatment with systemic corticosteroids or nonsteroidal immunosuppressive/immunomodulating medications (eg, cyclosporine, methotrexate, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors, biologic agents, etc.)

After the infection resolves and/or the laboratory 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

It is anticipated that approximately 420 patients will be eligible for this study. Eligible patients will be randomized in a 2:1:1:1 ratio to receive the same treatment regimen received in the initial treatment study (dupilumab 300 mg qw or 300 mg q2w), dupilumab 300 mg q4w, dupilumab 300 mg q8w, or matching placebo for 36 weeks according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated site personnel or clinical staff members. Randomization will be stratified according to the dupilumab regimen received in the initial treatment study, region (North America, Europe, Asia and Japan), and the baseline IGA scores (IGA=0 vs. IGA=1 vs. IGA>1; details will be specified in the IVRS/IWRS specifications document and will be documented in the clinical study report).

5.5.1. Blinding

Study patients, the investigators, sub-investigators, and all other study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Study Director, Medical Monitor, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

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.

Anti-drug antibody (ADA) 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 treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the treatment of 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 before unblinding the patient, whenever possible.

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

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

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

5.6.2. Supply and Disposition of Treatments

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

5.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each patient,

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

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

5.6.4. Treatment Compliance

All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors. Patients will complete a dosing diary to document compliance with self-injection of study drug.

5.7. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the end of the study 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

With the exception of TCS and TCIs, the following concomitant medications may not be used concomitantly with the study treatment through week 36. At the discretion of the investigator, patients are permitted to receive rescue treatment with some of the otherwise prohibited medications, as noted below. Rescue treatment (see Section 5.3 for details) should only be performed when medically necessary for worsening AD signs and/or symptoms requiring initiation or escalation of treatment.

- **Live (attenuated) vaccine**: If a live vaccine is necessary, study treatment will be stopped, optimally at least 12 weeks before vaccine administration, and may not be resumed for 12 weeks following vaccine administration.
- **Immunomodulating biologics** (other than dupilumab) may not be administered concomitantly with the study drug. If a biologic agent is administered during the study, study treatment must be immediately discontinued. In these cases, study treatment discontinuation is permanent, unless otherwise approved by the medical monitor.
- **Investigational drugs** (other than dupilumab) may not be administered concomitantly with the study drug. If an investigational drug is administered during the study, study treatment must be immediately discontinued. In these cases, study treatment discontinuation is permanent, unless otherwise approved by the medical monitor.
- **TCS or TCI** may be used during the study only if required for AD rescue (see Section 5.3). If TCS and/or TCIs are used during the study, study treatment should continue as planned.
- **Systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs** (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) may be used during the study only if required for AD rescue, or if medically needed to treat

concurrent conditions (eg, asthma). If these medications are used during the study, study treatment will be discontinued and may not resume sooner than 5 half-lives after the last dose of the respective corticosteroid or nonsteroidal immunosuppressive product.

- Any other medication or procedure intended to treat AD is prohibited, except those specifically permitted, ie, basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications

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 are permitted during the study.

For AD, permitted medications and procedures include basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anesthetics, topical and systemic 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.

5.7.3. 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 PROCEDURES

6.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: Schedule of Events

Study Procedure	**Treatment Period**										**Follow-up**		
Visit (V)	**Baseline V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**Primary Endpoint Visit V 10**	**V 11**	**End of Study V 12**	**Early Termination or Unscheduled Visit[4]**
Week (W)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W48**	
Day (D) Visit Window (d)	**D1[1]** **+/-3d**	**D29** **+/-3d**	**D57** **+/-3d**	**D85** **+/-3d**	**D113** **+/-3d**	**D141** **+/-3d**	**D169** **+/-3d**	**D197** **+/-3d**	**D225** **+/-3d**	**D253** **+/-3d**	**D281** **+/-7d**	**D337** **+/-7d**	
Screening/Baseline:													
Inclusion/Exclusion	X												
Informed Consent	X												
Demographics	X												
Concurrent illnesses	X												
Randomization	X												
Training on IVRS[2]	X[3]												
Treatment:													
Study drug dispensation[4]	X	X	X	X	X	X	X	X	X				
Study drug accountability		X	X	X	X	X	X	X	X	X			
Study drug administration[4]	X	Dupilumab or placebo, depending on treatment arm, through week 35											
Patient dosing diary[5]		X	X	X	X	X	X	X	X	X			
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy: [6]													
Pruritus NRS and Categorical Scale [7]	X	Weekly by patient diary, through the end of the study											

Study Procedure	**Treatment Period**										**Follow-up**		
Visit (V)	**Baseline V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**Primary Endpoint Visit V 10**	**V 11**	**End of Study V 12**	**Early Termination or Unscheduled Visit[4]**
Week (W)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W48**	
Day (D) Visit Window (d)	**D1[1]** **+/-3d**	**D29** **+/-3d**	**D57** **+/-3d**	**D85** **+/-3d**	**D113** **+/-3d**	**D141** **+/-3d**	**D169** **+/-3d**	**D197** **+/-3d**	**D225** **+/-3d**	**D253** **+/-3d**	**D281** **+/-7d**	**D337** **+/-7d**	
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, EQ-5D, HADS[8]	X			X			X			X		X	X
Patient Global Assessment of Disease	X			X			X			X		X	X
Patient Global Assessment of Treatment	X			X			X			X		X	X
ACQ-5, SNOT-22[8]	X									X		X	X
Well-controlled weeks (weekly diary)	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess sick leave/missed school days	X	X	X	X	X	X	X	X	X	X	X	X	X
Photograph AD area (select sites)[9]	X									X		X	X
Safety: [10]													
Weight	X									X		X	X
Height	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X											X	X
Electrocardiogram	X									X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	**Treatment Period**										**Follow-up**		
Visit (V)	**Baseline V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**Primary Endpoint Visit V 10**	**V 11**	**End of Study V 12**	**Early Termination or Unscheduled Visit[4]**
Week (W)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W48**	
Day (D) Visit Window (d)	**D1[1]** **+/-3d**	**D29** **+/-3d**	**D57** **+/-3d**	**D85** **+/-3d**	**D113** **+/-3d**	**D141** **+/-3d**	**D169** **+/-3d**	**D197** **+/-3d**	**D225** **+/-3d**	**D253** **+/-3d**	**D281** **+/-7d**	**D337** **+/-7d**	
Laboratory Testing[10]:													
Hematology	X			X			X			X		X	X
Chemistry	X			X			X			X		X	X
Urinalysis	X			X			X			X		X	X
Urine Pregnancy Test (WOCBP only) [11]	X	X	X	X	X	X	X	X	X	X		X	X
TARC	X			X			X			X		X	X
Total serum IgE	X			X			X			X		X	X
Antigen-specific IgE samples	X			X			X			X		X	X
Hs-CRP, ANA, anti-dsDNA, anti-TPO	X			X			X			X		X	X
Skin microbiome samples[12]	X			X			X			X		X	X
Research samples (serum/plasma)	X			X			X			X		X	X
PK/Drug Concentration and ADA Samples[10]:													
Functional dupilumab PK sample	X	X		X			X			X		X	X
Anti-dupilumab antibody sample[13]	X	X		X			X			X		X	X

1. All day 1 procedures overlap with procedures and assessments performed at week 16 in the initial treatment studies, and should be performed only once, with the exceptions of the informed consent procedure, IVRS training, measurement of height, and administration of study drug.

2. Patients will be trained to use the appropriate diary system to report pruritus and provide other information as required (eg, well-controlled weeks).
3. Patients will begin using the diary system at week 1.
4. At each study visit from day 1 through week 32, patients will be provided with a 4-week supply of study drug for administration outside the study site. The first injection will be administered at the study site. Patients will return the original kit boxes at each clinic visit. Study drug may also be dispensed during an unscheduled visit, if necessary.
5. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and any related issues; counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside the clinic.
6. Assessments/procedures should be conducted in the following order: patient reported outcomes, investigator assessments, safety and laboratory assessments, administration of study drug.
7. Patients will start calling the appropriate diary system at week 1.
8. 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). Asthma Control Questionnaire (ACQ-5) will be administered only to patients with a medical history of asthma. Sinonasal Outcome Test -22 (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.).
9. Select sites only – photograph AD area.
10. To be collected before the injection of study drug. Patients should be instructed to fast for 6 to 8 hours before blood sample collection. However, blood samples will be collected even if patients report to the study site without fasting. The status of the sample ("fasting" or "non-fasting") should be noted in the laboratory records.
11. A negative urine pregnancy test result is required before administration of study drug.
12. Noninvasive skin swabs; this may be performed at select sites only.
13. Patients who are ADA positive at their last study visit (early termination or end of study visit), and who do not participate in the open-label extension study, will be considered for follow-up based on their overall presentation at that time.

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

For laboratory testing, patients should be instructed to fast for 6 to 8 hours before blood sample collection. However, blood samples will be collected even if patients report to the study site without fasting. The status of the sample ("fasting" or "non-fasting") should be noted in the laboratory records.

6.2.1. Treatment Period

6.2.1.1. Visit 1 (Baseline)/Week 16 in the Initial Treatment Study/Day 1 (+/- 3 Days)

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

- Inclusion/exclusion
- Demographics
- Concurrent illnesses
- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus Numerical Rating Scale (NRS)
- Pruritus Categorical Scale
- IGA
- EASI
- Global Individual Signs Score (GISS)
- SCORing Atopic Dermatitis (SCORAD)
- Body surface area (BSA) of involvement of AD
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:

  - Patient Oriented Eczema Measure (POEM)
  - Dermatology Life Quality Index (DLQI)
  - EQ-5D
  - ACQ-5
  - SNOT-22
  - Hospital Anxiety and Depression Scale (HADS)
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Photograph of AD area (select sites only)
- Physical examination
- Weight
- Height
- Vital signs
- Electrocardiograms (ECGs)
- Laboratory testing
  - Hematology
  - Chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)
  - Thymus and activation-regulated chemokine (TARC)
  - Total serum IgE
  - Antigen-specific IgE
  - High sensitivity C-reactive protein (hs-CRP)
  - Anti-nuclear antibody (ANA)
  - Anti-double stranded DNA (Anti-dsDNA)
  - Anti-thyroid peroxidase antibody (Anti-TPO)
  - Skin microbiome samples (select sites only)
  - Research samples (serum/plasma)
  - Functional dupilumab pharmacokinetic (PK) sample
  - Anti-dupilumab antibody sample collection
- Randomization

- Training on IVRS
- Study drug administration
- Study drug dispensation

6.2.1.2. Visit 2/Week 4/Day 29 (+/- 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Vital signs
- Laboratory Testing
  - Urine pregnancy test (WOCBP only)
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample collection
- Study drug administration
- Study drug dispensation/accountability

6.2.1.3. Visit 3/Week 8/Day 57 (+/- 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)

- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Vital signs
- Laboratory testing
  - Urine pregnancy test (WOCBP only)
- Study drug administration
- Study drug dispensation/accountability

6.2.1.4. Visit 4/Week 12/Day 85 (+/- 3 Days)

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 treatment-emergent adverse events (TEAEs), or for other reasons.

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS

- SCORAD
- BSA of involvement of AD
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - DLQI
  - EQ-5D
  - collection
  - HADS
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- Vital signs
- 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
  - Research samples (serum/plasma)
  - Functional dupilumab PK sample
- Anti-dupilumab antibody sample collection
- Study drug administration
- Study drug dispensation/accountability

6.2.1.5. Visit 5/Week 16/Day 113 (+/- 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Vital signs
- Laboratory testing
  - Urine pregnancy test (WOCBP only)
- Study drug administration
- Study drug dispensation/accountability

6.2.1.6. Visit 6/Week 20/Day 141 (+/- 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA

- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Vital signs
- Laboratory testing
  - Urine pregnancy test (WOCBP only)
- Study drug administration
- Study drug dispensation/accountability

6.2.1.7. Visit 7/Week 24/Day 169 (+/- 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

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

- Patient Global Assessment of Treatment
- Vital signs
- 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
  - Research samples (serum/plasma)
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample collection
- Study drug administration
- Study drug dispensation/accountability

6.2.1.8. Visit 8/Week 28/Day 197 (+/- 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA

- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Vital signs
- Laboratory testing
  - Urine pregnancy test (WOCBP only)
- Study drug administration
- Study drug dispensation/accountability

6.2.1.9. Visit 9/Week 32/Day 225 (+/- 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Vital signs
- Laboratory testing
  - Urine pregnancy test (WOCBP only)
- Study drug administration
- Study drug dispensation/accountability

6.2.1.10. Visit 10/Week 36/Day 253 (+/- 3 Days) – Primary Endpoint Visit

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Check patient dosing diary
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
  - HADS
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- ACQ-5 (patients with asthma)
- SNOT-22
- Photograph of AD area
- Weight
- Vital signs
- ECGs

- 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
  - Research samples (serum/plasma)
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample collection
- Study drug accountability

6.2.1.11. Visit 11 (Follow-up)/Week 40/Day 281 (+/- 7 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD

- Vital signs

6.2.1.12. Visit 12 (End of Study)/Week 48/Day 337 (+/- 7 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Well-controlled weeks (weekly diary)
- Assess sick leave/missed school days

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
  - HADS
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- ACQ-5 (patients with asthma)
- SNOT-22
- Photograph of AD area
- Physical examination
- Weight
- Vital signs

- ECGs
- 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
  - Research samples (serum/plasma)
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample collection

6.2.1.13. Early Termination Visit

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Assess sick leave/missed school days
- Well-controlled weeks (weekly diary)

The following procedures and assessments will be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD

- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
  - HADS
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- ACQ-5 (patients with asthma)
- SNOT-22
- Photograph of AD area
- Physical examination
- Weight
- Vital signs
- ECGs
- 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
  - Research samples (serum/plasma)

  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample collection

6.2.1.14. Unscheduled Visit

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 TEAEs, or for any other reason.

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Assess sick leave/missed school days
- Well-controlled weeks (weekly diary)

The following procedures and assessments may be conducted:

- Pruritus NRS
- Pruritus Categorical Scale
- IGA
- EASI
- GISS
- SCORAD
- BSA of involvement of AD
- Administered only to the subset of patients who fluently speak a language in which the questionnaire has been translated:
  - POEM
  - DLQI
  - EQ-5D
  - ACQ-5
  - SNOT-22
  - HADS
- Patient Global Assessment of Disease
- Patient Global Assessment of Treatment
- ACQ-5 (patients with asthma)
- SNOT-22
- Photograph of AD area

- Physical examination
- Weight
- Vital signs
- ECGs
- 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
  - Research samples (serum/plasma)
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample collection

6.2.2. Early Termination Visit

Patients who are withdrawn from the study, either before or after the primary endpoint visit (week 36), will be asked to return to the clinic for an early termination visit, as described in Table 1. Patients who are ADA positive at their last study visit (early termination or end of study visit), and who do not participate in the open-label extension study, will be considered for follow-up based on their overall clinical presentation at that time.

6.2.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, to evaluate rescue treatment, or for any other reason as warranted. Assessments to be performed during unscheduled visit are shown in Section 6.2.1.14.

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: inclusion/exclusion criteria, demographics, height, and concurrent illnesses.

6.3.2. Efficacy Procedures

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 weekly recall period. Patients will access the IVRS, preferably around the same time, and be asked the following questions:

- 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 how your itch feels at its worst moment over the last 24 hours?"
- 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?"

Patients were instructed on using the IVRS to record their Pruritus NRS score during the screening visit of their initial study. They will continue to be queried by site staff for compliance at each scheduled (and any unscheduled) clinic visit. Patients will complete the rating scale at time points according to Section 6.2.

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 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 were instructed on using the IVRS to record their Pruritus NRS score during the screening visit of their initial study and will be queried by site staff for compliance at each scheduled (and any unscheduled) clinic visit. Patients will complete the categorical scale at time points according to Section 6.2.

6.3.2.3. Investigator's Global Assessment

The IGA is an assessment scale 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.

6.3.2.4. 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, and 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.

6.3.2.5. 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.

6.3.2.6. 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 6.3.2.7) 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 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: $A/5 + 7B/2 + C$ 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.

6.3.2.7. 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.

6.3.2.8. 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; 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 POEM is provided in the study reference manual.

6.3.2.9. 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.

6.3.2.10. 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 (EQ VAS). 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, ie, a unique health state is defined by combining 1 level from each of the 5 dimensions. Overall health state is referred to in terms of a 5-digit code. A total of 243 possible health states can be defined this way. For example, state 11111 indicates no problems in any of the dimensions, whereas state 11223 indicates no problems with mobility and self-care, some problems with performing usual activities, moderate pain or discomfort, and extreme anxiety or depression. Two further states (unconscious and death) are included in the full set of 245 EQ-5D health states.

The EQ VAS 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.

6.3.2.11. 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.

6.3.2.12. 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.

6.3.2.13. 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.

6.3.2.14. Juniper Asthma Control Questionnaire

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

6.3.2.15. 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.

6.3.2.16. Well-Controlled Weeks

During their weekly IVRS call completion, patients will be asked: "Has your eczema been well-controlled over the last week?" Answer options will be "Yes" and "No." For the purpose of this protocol, well-controlled weeks are those for which patients answer "Yes" AND during which no rescue treatments were administered.

6.3.2.17. 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.

6.3.2.18. 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 of this study/week 16 in the initial studies. Subsequent photographs of the same area will be taken at week 36 (end of treatment) and week 48 (end of study).

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

6.3.3. Safety Procedures

6.3.3.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected predose at time points according to Section 6.2.

6.3.3.2. 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.

6.3.3.3. Weight and Height

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

6.3.3.4. Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Section 6.2.

Heart rate will be recorded from the ventricular rate, and the PR, QRS, RR and QT intervals will be recorded. Electrocardiogram results will be interpreted by a central reading center. Instructions for performing the assessment and for transmitting ECG data are provided in the study reference manual. The ECG strips or reports will be retained with the source and results will be recorded in the case report form (CRF).

6.3.3.5. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. 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.

Patients should be instructed to fast for 6 to 8 hours before blood sample collection. However, blood samples will be collected even if patients report to the study site without fasting. The status of the sample ("fasting" or "non-fasting") should be noted in the laboratory records. Detailed instructions for blood sample collection are provided in the laboratory manual.

Samples for laboratory testing will be collected at visits 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 (BUN)	Low-density lipoprotein
Carbon dioxide	AST	High-density lipoprotein
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[2]

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

[2] CPK isoenzymes will be reflexively 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 (urine) for women of childbearing potential will be performed at time points according to Section 6.2.

Additional tests may be required to verify eligibility, or to clarify or help manage AEs. Any laboratory tests that are not specifically noted in the protocol require written approval from the medical monitor.

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

Any unused serum samples collected for ADA measurements may be used for exploratory immunogenicity analysis, drug concentration assessments, exploratory biomarker research, or to investigate unexpected AEs (see Section 6.3.5).

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 and may be banked to study the effects of the study drug on modulation of IL-4Rα, atopic disease processes, and response to treatment (efficacy and toxicity). Unused samples collected for drug concentration or ADA analyses may also be used for 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. Exploratory Biomarker Testing

Biomarker samples being collected in this study are: TARC, total serum IgE, antigen-specific IgE (region-specific, allergen-specific panels), hs-CRP, ANA, anti dsDNA, anti-TPO, and skin microbiome. Samples will be collected at time points according to Section 6.2. These are exploratory assessments [redacted] 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 PD effect of the drug. [redacted]. 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. [redacted]

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. [redacted]

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.

Skin microbiome samples may be collected and banked at a subset of sites in order to study the relationship of the microbiome (eg, diversity and/or colonization) with maintenance of AD disease control.

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 preexisting condition that is temporally associated with the use of the study drug.

7.1.2. Serious Adverse Event

A serious adverse event (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 120 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE.

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

Adverse events of special interest for this study include:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Severe injection site reactions 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/antiviral/antifungal agent; any infection requiring treatment with oral antibiotic/antiviral/antifungal for longer than 2 weeks; any clinical endoparasitosis; any opportunistic infection

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

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 assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

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

The possible answers are:

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

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

For a list of factors to consider in assessing the relationship of AEs to study drug, see Appendix 1.

The 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) 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 concomitant medications and treatment, concurrent illnesses, and weight. Information on patient age and sex will be obtained from the initial treatment studies.

8.2. Primary and Secondary Endpoints

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

Co-primary endpoints:

- Difference between current study baseline and week 36 in percent change in EASI from the baseline of the initial treatment study (R668-AD-1334 or R668-AD-1416)
- Percent of patients maintaining EASI-75 at week 36 in the subset of patients with EASI-75 at baseline

Key secondary endpoints:

- Percent of patients with an increase of ≥2 points in IGA from baseline to week 36, in the subset of patients with IGA (0,1) at baseline
- Percent of patients with IGA(0,1) at week 36 in the subset of patients with IGA(0,1) at baseline
- Percent of patients whose peak Pruritus NRS increased by 3 or more points from baseline to week 36 in the subset of patients with peak Pruritus NRS ≤7 at baseline

Other secondary endpoints:

- Percent of patients with IGA increase of ≥2 points from baseline through week 36 in the subset of patients with IGA ≤2 at baseline
- Time to first IGA increase of ≥2 points from baseline in the subset of patients with IGA(0,1) at baseline

- Percent of patients with IGA(3,4) in the subset of patients with IGA(0,1) at baseline
- Percent of patients with EASI-50 (≥50% reduction in EASI score from the baseline of the initial treatment study) through week 36
- Absolute change from baseline to timepoints through week 36 in
  - EASI
  - SCORAD
  - Peak Pruritus NRS
  - BSA
  - POEM
  - DLQI
- Difference between current study baseline and timepoints through week 36 in percent change in SCORAD from the baseline of the initial treatment study
- Difference between current study baseline and timepoints through week 36 in percent change in Peak Pruritus NRS from the baseline of the initial treatment study
- Rate of flares (defined as worsening of disease requiring initiation or escalation of rescue treatment)
- Proportion of well controlled weeks
- Incidence of skin infections

8.3. Pharmacokinetic Variables

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

- C_{trough}
- C_{last}
- T_{last}
- T_{max}
- Time to steady state
- C_{ss} - steady state concentration

8.4. Anti-Drug Antibody Variables

Anti-drug antibody 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 pre-existing immunoreactivity[†]

- Total subjects with treatment-emergent response ‡
- Total subjects with treatment-boosted response*
- The treatment-emergent responses will be further categorized into Persistent, Indeterminate, and Transient responses using the following definitions:
  - Persistent response –a treatment-emergent response with 2 or more consecutive ADA positive sampling time points, separated by a greater than (>) 12-week period, with no ADA negative samples in between the 12-week period
  - Indeterminate response –a treatment-emergent response in which only the last collected sample is positive in the ADA assay
  - Transient response- a treatment-emergent response that is not considered persistent or indeterminate
- Titer values categories
  - Low Titer < 1000)
  - Moderate (1,000 ≤ Titer ≤ 10,000)
  - High (Titer > 10,000)
- Total subjects positive in the Neutralizing Antibody Assay at any time point analyzed (for ADA-positive samples)

†Preexisting immunoreactivity is defined as either an ADA-positive response in the ADA assay at baseline, with all post-first dose ADA results being negative, or an ADA-positive response at baseline, with all post-first dose ADA responses being less than 4-times the baseline titer levels.

‡Treatment-emergent response is defined as a positive response in the ADA assay, post-first dose, when baseline results are negative or missing.

*Treatment-boosted response is defined as a positive response in the ADA assay, post-first dose, which is greater than or equal to 4-times the baseline titer levels, when baselines results are positive.

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 of the dupilumab treatment groups (300 mg qw or 300 mg q2w, 300 mg q4w, and 300 mg q8w):

H0: No treatment difference between dupilumab and placebo

H1: There is a treatment difference between dupilumab and placebo

The baseline IGA scores (IGA=0 vs. IGA=1 vs. IGA >1) and region (North America, Europe, Asia, and Pacific Asia including Japan) will be the 2 stratification factors for patient randomization and will be accounted for in the statistical modeling for efficacy.

9.2. Justification of Sample Size

It is estimated that approximately 420 patients will be enrolled in the study. The number of patients enrolled in this study depends on the number of patients and the responder rates in the two 16-week initial treatment studies (R668-AD-1334 and R668-AD-1416).

Assumptions used to calculate power for the co-primary endpoints are informed by data from completed dupilumab studies. They are as follows:

- Test (T) 1: Mean difference (baseline to week 36) in % change in EASI
  - Dupilumab (300 mg qw or 300 mg q2w): 5%
  - Placebo: 35%
- T2: Percent of patients with EASI-75 at week 36
  - Dupilumab (300 mg qw or 300 mg q2w): 85%
  - Placebo: 30%

It is estimated that, with the current sample size, 170 patients in the dupilumab 300 mg qw or q2w group, and 84 patients in the placebo group from each of the initial treatment dosing, the study will provide 99% power at the 2-sided 5% significance level to detect the expected differences between dupilumab and placebo for the co-primary endpoints for comparisons included in the testing hierarchy.

9.3. Analysis Sets

9.3.1. Efficacy Analysis Set

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

The per protocol set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. A major protocol violation is one that may affect the interpretation of study results. 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 amount of study drug; it is based on the treatment received (as treated). The details of as-treated definition are to be specified in the SAP. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

9.3.3. Other Analysis Sets

9.3.3.1. Pharmacokinetic Analysis Set

The PK analysis set (PKAS) includes all treated patients who received any amount of study drug and who had a qualified result for drug concentration on day 1 (baseline) and at least 1 qualified result following the first dose of study drug.

9.3.3.2. Anti-Drug Antibody Analysis Set

The ADA analysis set (ADAAS) includes all treated patients who received any study drug and who had at least 1 qualified ADA result in the ADA assay following the first dose of the study drug.

9.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: 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.

9.4.1. Patient Disposition

The following will be provided:

- The total number of randomized patients (who received a randomization number)
- The total number of patients in each analysis set (eg, FAS, provided in Section 9.3.1)
- 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

9.4.2. 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.

9.4.3. Efficacy Analyses

Treatment differences will be tested for each of the dupilumab treatment groups (300 mg qw, 300 mg q2w, 300 mg q4w, and 300 mg q8w) compared with placebo.

For the comparisons of dupilumab treatment groups vs. placebo, a hierarchical testing procedure with an alpha level of 0.05 will be adopted for the primary and key secondary efficacy endpoints in a prespecified order:

- T1: Mean difference (baseline to week 36) in % change EASI
- T2: Percent of patients with EASI-75 at week 36
- T3: Percent of patients with an increase of ≥ 2 points in IGA from baseline to week 36, in the subset of patients with IGA (0,1) at baseline
- T4: Percent of patients with IGA=0 or 1 at week 36 for patients with IGA=0 or 1 at baseline
- T5: Percent of patients with peak Pruritus NRS increased by ≥3 points from baseline to week 36

If an endpoint is significant at a 2-sided 0.05 level, the sequential analysis will continue for the next endpoint until the significance level is no longer met.

If all tests are significant from the primary to key secondary endpoints, the same hierarchical testing procedure will apply to dupilumab 300 mg q4w vs. placebo and then dupilumab 300 mg q8w vs. placebo. The testing order will be as follows:

1. High dose group (300 mg qw or q2w) vs placebo: in the order of T1, T2, T3, T4, then T5; then
2. Middle dose group (300 mg q4w) vs placebo: in the order of T1, T2, T3, T4, then T5; then
3. Low dose group (300 mg q8w) vs placebo: in the order of T1, T2, T3, T4, then T5

To account for the impact of rescue medication on efficacy:

- For binary response endpoints, a patient who received any rescue medication will be specified as a nonresponder from the time the rescue medication is used.
- For continuous endpoints, data after rescue treatment will be set to missing.
- If a patient withdraws from the study, this patient will be counted as a nonresponder for binary endpoints after withdrawal.

9.4.3.1. Primary Efficacy Analysis

The difference between baseline and week 36 in percent change in EASI from baseline of studies R668-AD-1334 or R668-AD-1416 will be analyzed in FAS by using the multiple imputation (MI) with analysis of covariance (ANCOVA) model. Graphs of least-square (LS) means ±SE by visit for change from baseline related variables will be presented.

Missing data will be imputed using the MI with ANCOVA model for the primary analysis. Patients' efficacy data through week 36 after the rescue medication usage will be set to missing first, and then be imputed by the MI method. Missing data will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI following the 2 steps below:

- Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure. 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 (disease severity), and relevant baseline.

Each of the 40 complete datasets will be analyzed using an ANCOVA model with treatment, randomization strata (disease severity: baseline IGA=0 vs. IGA=1 vs. IGA >1, and region: Americas, Europe, and Asia Pacific including Japan), and relevant baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.

The imputation model will include:

- The covariates included in the ANCOVA model, including treatment group, baseline value, and the randomization strata
- Measured endpoint values from every clinic visit up to week 36

Randomization strata in the efficacy analyses will be based on the data collected by the interactive voice response system (IVRS).

Sensitivity analyses may be performed; details will be included in the SAP, which will be finalized before the database is locked. One sensitivity analysis for the primary endpoint will be performed using a mix-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.

For the binary co-primary endpoint (percent of patients maintaining EASI-75 at week 36 in the subgroup of patients with EASI-75 at study baseline), the Cochran-Mantel-Haenszel test adjusted by randomization strata (disease severity: baseline IGA=0 vs. IGA=1 vs. IGA>1, and region: Americas, Europe, and Asia Pacific including Japan) will be used. This analysis may also be performed for all randomized patients. To account for the impact of rescue medication on the efficacy effect, if rescue medication is used, the patient will be specified as a nonresponder from the time rescue medication is used. If a patient withdraws from the study, this patient will be counted as a nonresponder after withdrawal.

Sensitivity analyses may be performed; details will be included in the SAP, which will be finalized before the database is locked. As a sensitivity analysis for the primary endpoint, data after administration of rescue medication will not be censored.

9.4.3.2. Key Secondary Efficacy Analysis

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

9.4.3.3. Other Secondary Analysis

For similar binary and continuous other secondary endpoints, unless otherwise specified in the SAP, the exploratory analysis will use the same approach as those used for primary and key secondary endpoints. No sensitivity analysis will be performed for exploratory endpoints.

For time-to-event endpoints, the log rank test stratified by the randomization strata will be used. The Kaplan-Meier curve will be provided.

9.4.4. Safety Analysis

Safety analysis will be based on the SAF with the 300 qw and 300 q2w doses combined. This includes reported TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and 12-lead ECG results).

9.4.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the informed consent form (ICF) to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to week 36 (day 253) or day of permanent withdraw from study treatment, whichever comes earlier.
- Overall study period (on-treatment and follow-up period) is defined as the period from the administration of first study dose to the last study visit.

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

Analysis

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

Summaries of all TEAEs by treatment group will 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.

9.4.4.2. 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.

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 potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test.

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

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

9.4.4.3. Treatment Exposure

The duration of treatment 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.

9.4.4.4. Treatment Compliance

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%.

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

9.4.5. Analysis of Drug Concentration Data

The following analyses based on sparse sampling may be conducted:

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

Descriptive statistics of the calculated PK parameter specified in Section 8.3.

No formal statistical analysis will be performed.

9.4.6. Analysis of Anti-Drug Antibody Data

The ADA variables will be summarized using descriptive statistics by dose groups in the ADA analysis set. Frequency tables of the proportion of patients developing ADA positivity in the ADA assay, neutralizing antibody (NAb) status in the NAb assay, pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent, indeterminate and transient ADA responses. Titers will be presented as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Plots of drug concentrations will be examined, and the influence of ADAs on individual PK profiles will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

9.5. 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 predose assessment available.

General rules for handling missing data:

- Rules for handling missing data for efficacy assessments
- 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 signs data, or physical examination data will be made.

Visit windows:

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

Unscheduled assessments:

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

9.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

The CRF data for this study will be collected with an electronic data capture (EDC) tool.

10.2. Electronic Systems

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

- IVRS/IWRS system – randomization, study drug supply
- Electronic diary – collection of Pruritus NRS and well-controlled weeks
- EDC system – data capture/uploading and storing photographs
- Statistical Analysis Software (SAS) – statistical review and analysis
- ARGUS – PVRM Safety System
- nQuery Advisor – sample size calculations

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, 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

Akhavan A, Rudikoff D. Atopic dermatitis: systemic immunosuppressive therapy. Semin Cutan Med Surg 2008; 27:151-155.

Badia X, Mascaro JM, et al. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. Br J Dermatol 1999; 141:698-702.

Bieber T. Mechanisms of disease: atopic dermatitis. N Engl J Med 2008; 358:1483-94.

Charman CR, Venn AJ, et al. The patient-oriented eczema measure. Arch Dermatol 2004; 140:1513-1519.

Hanifin JM, Thurston M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001; 10: 11-18.

Hart TK, Blackburn MN et al. Preclinical efficacy and safety of pascolizumab (SB 240683): a humanized anti-interleukin-4 antibody with therapeutic potential in asthma. Clin Exp Immunol 2002;130:93-100.

Herrmann C. International experiences with the hospital anxiety and depression scale – a review of validation data and clinical results. J Psychosom Res 1997;42(1):17-41.

Kaufmann R, Bieber T, Helgesen AL et al. Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: a randomized trial. Allergy 2006;61:375-381.

No authors listed. Severity scoring of atopic dermatitis: the SCORAD index: consensus report of the European task force on atopic dermatitis. Dermatology 1993;186: 23-31.

Schmitt J, Schakel K, et al. Prednisolone vs. cyclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. Brit J Dermatol 2009; journal compilation:1-8.

Schmitt J, Schmitt N, et al. Cyclosporin in the treatment of patients with atopic eczema-a systematic review and meta-analysis. JEADV 2007; 21: 606-619.

Schram ME, Spuls PI, et al. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy 2012; 67:99-106.

Wenzel S, Wilbraham D, et al. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. Lancet 2007; 370:1422-1431.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-370.

21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of Multiple Dupilumab Dose Regimens Administered as Monotherapy for Maintaining Treatment Response in Patients with Atopic Dermatitis, dated 12 October 2016, 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 treatments being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a known response to the study drug based upon preclinical data or prior clinical data

Yes:

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

NOTE: This list is not exhaustive.

STATISTICAL ANALYSIS PLAN

Title: A phase 3, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of multiple Dupilumab dose regimens administered as monotherapy for maintaining treatment response in patients with atopic dermatitis

Protocol: R668-AD-1415

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

Version: Final

Date: October 24, 2016

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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
IVRS	Interactive voice response 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

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-1415 study.

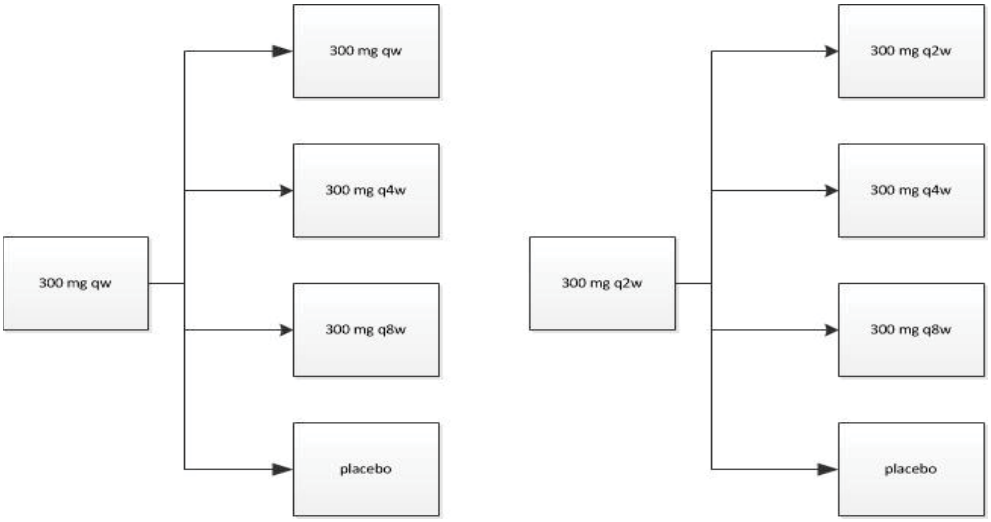
This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. The SAP will be based on blinded review of the study and data. This plan will be finalized prior to the final database lock.

1.1. Background and Rationale

This is a phase 3 study to determine the ability of different dupilumab dose regimens, administered as monotherapy, to maintain treatment responses achieved after an initial 16-week treatment with dupilumab monotherapy in patients with moderate-to-severe AD, inadequately controlled with topical medications.

Patients enrolled in this study are those who achieved treatment success criteria (Investigator's Global Assessment [IGA] 0 or 1 or Eczema Area and Severity Index [EASI]-75, ≥75% improvement) after receiving dupilumab (300 mg weekly [qw] or 300 mg every 2 weeks [q2w]) for 16 weeks in 2 parent studies (SOLO1:R668-AD-1334 or SOLO2:R668-AD-1416). The purpose of the study is to determine the ability of different dupilumab dose frequency regimens of equal or less intense frequency are able to maintain treatment response over a period of 36 weeks.

The study is designed as a randomized dose frequency reduction/dose withdrawal clinical investigation. Eligible patients will be randomized on day 1 (i.e. week 16 of the parent studies) to either continue the same dose regimen received in the initial treatment study (300 mg qw or 300 mg q2w), to step down to lower dose frequency regimens (300 mg every 4 weeks [q4w] or 300 mg every 8 weeks [q8w]), or to discontinue dupilumab and receive placebo during the current study (See the chart below).



To maintain the blinding of the parent studies, patients who received placebo and achieved treatment success criteria (IGA scores of 0 or 1 (IGA(0,1)) or EASI-75) in the parent studies will also be enrolled in the current study, but they will not be randomized; these patients will constitute a separate cohort and still receive placebo during the entire 36-week study treatment period. These patients will not be included in any analysis sets.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to assess the ability of different dupilumab dose regimens, administered as monotherapy, to maintain the treatment response achieved after 16 weeks of parent studies with dupilumab monotherapy compared to placebo.

1.2.2. Secondary Objectives

The secondary objective of the study is to assess the safety of different dupilumab dose regimens administered as monotherapy over a period of 36 weeks.

1.3. Modifications from the Statistical Plan in the Final Protocol

The summary of modifications is listed in the following table.

Item	Protocol Section	Description
1	8.2	For the key secondary "Percent of patients with an increase of ≥2 points in IGA from baseline to week 36 in the subset of patients with IGA(0,1) at baseline" the wording will be rephrased to: Percent of patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with IGA(0,1) at baseline.

2	8.2	For one of other secondary endpoints, Percent of patients with IGA increase of ≥2 points from baseline through week 36 in the subset of patients with IGA ≤2 at baseline, this endpoint will be removed.
3	8.2	Add one endpoint in the section of other secondary endpoints: Absolute change in HADS from baseline through week 36
4	9.3.3.1	The definition of pharmacokinetic analysis set is modified to: The PK population includes all treated patients who received any amount of study drug and who had at least 1 non-missing drug concentration following the first dose of study drug.
5	9.3.3.2	For clarification, the ADA analysis set (ADAAS) includes all treated patients who received any study drug and who had at least 1 qualified ADA result in the ADA assay following the first dose of the study drug will be rephrased to: The ADA population includes all treated patients who received any study drug and who had at least 1 non-missing ADA result in the ADA assay following the first dose of the study drug.

1.4. Modifications from the Previously Approved SAP

Not applicable.

2. INVESTIGATIONAL PLAN

2.1. Study Design and Randomization

This is a phase 3, randomized, double-blind, placebo-controlled study to determine the ability of different dupilumab dose regimens to maintain the treatment response achieved by patients with AD after an initial 16-week treatment with dupilumab monotherapy in 1 of 2 parent studies (R668-AD-1334 or R668-AD-1416).

To be eligible for this maintenance study, all patients must have achieved an IGA 0 or 1 (IGA(0,1)) or EASI-75 at week 16 in either parent study after treatment with 300 mg qw subcutaneous (SC) or 300 mg q2w SC.

Eligible patients who did not receive placebo in the initial studies will be randomized 2:1:1:1 to 1 of the following 2 treatment groups, depending on the dose of dupilumab received in the parent study (300 mg qw SC or 300 mg q2w SC). Randomization assigned each of the treatment groups described in the chart of Section 1.1 will be stratified according to region (North America vs. Europe vs. Asia Pacific vs. Japan) and baseline IGA scores (IGA=0 or 1 vs. IGA >1).

Patients who received 300 mg qw SC or 300 mg q2w from the parent studies will be randomized 2:1:1:1 to receive 1 of the following 4 treatment regimens:

- Dupilumab 300 mg qw SC
- Dupilumab 300 mg q4w SC
- Dupilumab 300 mg q8w SC
- Placebo

2.2. Sample Size and Power Considerations

Based on the number of eligible patients from the parent studies (R668-AD-1334 and R668-AD-1416), approximately 420 patients are expected in this study. Assumptions used to calculate power for the co-primary endpoints regarding the comparisons between dupilumab 300 mg qw or dupilumab 300 mg q2w and placebo were informed by the data from completed dupilumab studies. The tests are as follows:

Test 1(T1): Mean difference (baseline to week 36) in percent change in EASI compared to EASI in the parent study (population: all randomized patients in FAS)

- Dupilumab (300 mg qw or q2w): mean (SD) = 5% (13%)
- Placebo: mean (SD) = 35% (25%)

Test 2(T2): Percent of patients with EASI-75 at week 36 (population: randomized patients with EASI-75 at baseline (week 0))

- Dupilumab (300 mg qw or q2w): 85%
- Placebo: 30%

It is estimated that with the current sample size, 170 patients in the dupilumab 300 mg qw or q2w group, and 84 patients in the placebo group from each of the parent dosing regimens, the study will provide 99% power at 2-sided 5% significance level to detect the expected differences between dupilumab and placebo for the co-primary endpoints.

2.3. Study Plan

The study consists of a 36-week treatment period and a 12-week follow-up period. A study flow diagram is below:

Treatment Period (Study Weeks, Days)				**Follow-Up**	
V1	V2	V3-V10 (q4w)		V11	V12
Baseline					End of Study
(Day 1*)	W4 (Day 29)	W8-W32 (Day 57-Day 225)	W36** (Day 253)	W40 (Day 281)	W48 (Day 337)

*Week 16 in the parent studies – R668-AD-1334 or R668-AD-1416
**Patients will receive weekly study drug (dupilumab and/or placebo, depending on their treatment arm) for 36 weeks

Following randomization on day 1 (which is the week 16 visit in the parent studies), patients will begin study treatment. Patients will return to the clinic every 4 weeks (at weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36). Patients will continue to receive study drug (dupilumab or placebo) weekly for 36 weeks. Patients randomized to q2w, q4w, and q8w regimens will receive placebo during weeks when dupilumab is not administered.

Patients who complete the 36-week treatment period may enroll in an open-label extension (OLE) study starting at week 36 or anytime thereafter. Patients who do not transition into OLE at week 36 will enter the follow-up period, which includes two additional visits: one at week 40 and a final (end of study) visit at week 48. Patients will complete the applicable follow-up visits until they enroll in the OLE.

For the purpose of maintaining the blind of the treatment in the parent studies, placebo responders (defined as patients who received placebo and who achieved an IGA 0 or 1 or EASI-75 at week 16 in the parent studies) will also be eligible to enroll in the current study, but they will not be randomized; these placebo responder patients will receive placebo during the entire 36-week treatment period in this study, but will constitute a separate treatment group and will not be included in any analysis set for this maintenance study.

If medically necessary (e.g., to control intolerable AD symptoms), patients may receive rescue treatment for AD symptoms.

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 at randomization (as randomized).

Two additional subsets of FAS are further defined:

- patients with IGA(0,1) at baseline (week 0) for all IGA related endpoints in secondary endpoints
- patients with EASI-75 at baseline (week 0) for the primary endpoint: percent of patients maintaining EASI-75 at week 36

3.2. Per Protocol Analysis Set (PPS)

The per protocol set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. A major protocol violation is one that may affect the interpretation of study results. 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 (i.e. inclusion criteria #2)
- The percentage of a patient's compliance with study drug injection is <80% or >120% of the scheduled doses during the study treatment period

3.3. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients excluding patients receiving placebo in parent studies who received any amount of study drug; it is based on the treatment received (as treated).

The as-treated treatment group is defined based on treatment completers and non-completers by the following rules:

- For patients who completed the treatments period per protocol (completers), which means that he/she received the study treatment at week 35 the planned number of dupilumab doses per regimen and the interval for the actual number of dupilumab doses per corresponding as-treated regimen will be constructed as follows:

Potential Regimen	Planned # of Dupilumab Doses	Interval for Actual # of Dupilumab Doses per Corresponding As-Treated Regimen
300 mg qw	36	≥27
300 mg q2w	18	≥14 – 27
300 mg q4w	9	≥7-14
300 mg q8w	5	≥1-<7
Placebo	0	<1

The as-treated regimen will be determined by checking which interval contains the actual number of dupilumab doses injected.

- For patients who discontinued the treatment prior to week 35 (non-completers) the expected number of dupilumab doses will be derived based on the known scheduled visit (Week X) for the last treatment injection or actual on-treatment interval if the last treatment injection is unscheduled.

If the last treatment injection occurs at Week Y, the expected number of dupliumab doses is as follows:

Potential Regimen	Expected # of Dupilumab Doses	Interval for Actual # of Dupilumab Doses per Corresponding As-Treated Regimen
300 mg qw	E1=Y+1	≥(E1+E2)/2
300 mg q2w	E2=Floor(Y/2)+1	≥(E2+E3)/2 - < (E1+E2)/2
300 mg q4w	E3=Floor(Y/4)+1	≥(E3+E4)/2 - < (E2+E3)/2
300 mg q8w	E4=Floor(Y/8)+1	≥1 - < (E3+E4)/2
Placebo	0	<1

Note: Define floor(X) as the largest integer leas than (X) (e.g. If X=8.4, floor(X)=8)

The as-treated regimen will be determined based on the interval that contains the actual number of dupilumab doses.

- If the last treatment was an unscheduled one, the actual on-treatment interval U will be calculated by (date of last study treatment-date of first study treatment +1).
  - If 1≤U<12, the as-treated regimen will be the randomized regimen. For patients randomized to placebo regimen and received a dose of dupilumab the as treatment regimen will be 300 mg q8w; if received 2 dupilumab doses, the as-treated regimen is 300 mg qw.
  - If U≥12, the expected number of dupilumab doses for each regimen will be derived as follows:

Potential Regimen	**Expected # of Dupilumab Doses**	**Interval for Actual # of Dupilumab Doses per Corresponding As-Treated Regimen**
300 mg qw	E1=Floor(U/7)+1	≥(E1+E2)/2
300 mg q2w	E2=Floor(U/14)+1	≥(E2+E3)/2 - <(E1+E2)/2
300 mg q4w	E3=Floor(U/28)+1	≥(E3+E4)/2 – <(E2+E3)/2
300 mg q8w	E4=Floor(U/56)+1	≥1 - <(E3+E4)/2
Placebo	0	<1

Note: Assume E1-E4 are different.

  - If there are multiple regimens with the same expected number of dupilumab doses causing multiple same intervals, the as-treated regimen will be the randomized regimen if the actual number of dupilumab doses is the same as the expected number of dupilumab doses; otherwise, the as-treated regimen will be determined by the interval containing the actual number of dupilumab doses.

    Example 1: For an early discontinuation patient randomized to 300 mg q4w with U=13 and received 1 dupilumab doses, the expected number of dupilumab doses per regimen is as follows:

Potential Regimen	**Expected # of Dupilumab Doses**	**Interval for Actual # of Dupilumab Doses per Corresponding As-Treated Regimen**
300 mg qw	2	≥1.5
300 mg q2w	1	≥1 - <1.5
300 mg q4w	1	1
300 mg q8w	1	1
Placebo	0	0

    There are three regimens sharing the same expected number of dupilumab doses. The expected number of dupilumab doses for the randomized regimen 300 mg q4w is the same as the actual number of dupilumab doses. Therefore, the as-treated regimen is still 300 mg q4w.

Example 2: For an early discontinuation patient randomized to 300 mg q4w with U=60 and actually received 3 dupilumab doses, the as-treatment regimen will be still 300 mg q4w based on the corresponding interval contained 3actual dupilumab doses.

Potential Regimen	Expected # of Dupilumab Doses	Interval for Actual # of Dupilumab Doses per Corresponding As-Treated Regimen
300 mg qw	Floor(60/7)+1=9	≥7
300 mg q2w	Floor(60/14)+1=5	≥4 - <7
300 mg q4w	Floor(60/28)+1=3	≥2.5 – <4
300 mg q8w	Floor(60/56)+1=2	≥1 - <2.5
Placebo	0	<1

Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.4. The Pharmacokinetic Analysis Set (PKAS)

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

3.5. The ADA Analysis Set (ADAAS)

The ADA population includes all treated patients who received any study drug and who had at least 1 non-missing ADA result in the ADA assay following the 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 baseline 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 including Japan, Europe), Baseline weight with grouping (kg, <70; ≥70-<100, ≥100), Height (m), and BMI (kg/m^2; <15, ≥15-<25, ≥25-<30, ≥30)
- Baseline characteristics: Duration of historical AD disease (year; <26, ≥26 years) from SOLOs studies, Investigator's Global Assessment (IGA) score (0-4), EASI-75 (Yes/No), IGA>1 and EASI-75=Yes, IGA(0,1) and EASI-75=Yes, IGA(0,1) and EASI-75=No, EASI scores, percent change in EASI from parent study baseline, Pruritus numerical rating scale (NRS) for maximum or average itch intensity, SCORing Atopic Dermatitis (SCORAD) score, Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure (POEM), Body Surface Area (BSA)

Involvement of Atopic Dermatitis, and Hospital Anxiety and Depression Scale (HADS)

Unless otherwise specified, the baseline is referring to the current study baseline.

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. 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 in SOLO-1 or SOLO-2 clinical trial is also collected with information of number of AD flares and episodes of skin infections requiring pharmacological treatment.

Both of medical history and atopic disease medical history records have been collected in SOLO-1 and SOLO-2 clinical trials.

4.3. Pre-treatment/ Concomitant Medications and Procedures

Medications/Procedures will be recorded from the time of informed consent to the final study visit. This includes medications/procedures that were started before the study and are ongoing during the study.

Medications will be coded to the anatomical therapeutic chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to the first dose of the study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the final study visit.

The observation period of concomitant medications/procedure will be divided into two periods: on-treatment, and overall study period:

- The on-treatment period is defined as the period from day 1 to week 36 (day 253) or day of permanently withdraw from treatment, whenever earlier.
- Overall study period (on-treatment and follow-up period) is defined as the period from the administration of first study dose to the last study visit.

Background treatment: Patients are required to continue applying moisturizers (emollients) that were initiated before day 1, at least twice daily throughout the study (all 48 weeks where applicable). The compliance of moisturizers (emollients) used from day 1 to the end of study, defined as (the number of moisturizers used reported via IVRS during the treatment period)/(number of weekly reports through IVRS within the treatment period)x100%, will be derived.

Prohibited medications and procedures: medications/procedures are described in the section 5.7.1 of the protocol. They will be identified by a blinded adjudication. In addition, the following concomitant procedures are prohibited during study participation:

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

Rescue treatment for AD: If medically necessary (e.g., to control intolerable AD symptoms), rescue treatment for AD with otherwise prohibited medications (see above) may be provided to study patients, at the discretion of the investigator. The algorithm for identifying the rescue treatments has been specified in Appendix 10.5. For the purpose of analyzing the primary and key secondary efficacy endpoints, patients who receive rescue treatment during the study treatment period will be considered study treatment failures, but they may continue study treatment if rescue consists of topical treatments.

Time to the first rescue treatment (weeks) will be derived per patient defined as (date of receiving the first rescue medication – first study treatment administration date +1)/7 if any rescue medications were administered or (last study visit date – first study treatment date +1)/7 if no any rescue medications were administered.

A corresponding censoring variable regarding to time to first rescue medication will be set to 1 if that patient did not receive any rescue treatments; otherwise, 0 if that patient received a rescue treatment.

If a medication was taken or procedure performed prior to administration of the study drug and ended after the first administration of study drug or is still ongoing, this medication or procedure will be flagged as both of pre-treatment and concomitant medication/procedure.

Study day onset will be derived as follows: 1) for medications/procedures started before study treatment, the study day onset = date of medication/procedure start - date of the first study treatment; 2) for medications/procedures started on or after study treatment, the study day onset = date of medication start - date of the first dose+1.

4.4. Efficacy Variables

Unless otherwise specified, the baseline in this section is referring to the current study baseline (week 0) that is defined as the last observed value from the parent study.

4.4.1. Primary Efficacy Variable

The co-primary endpoints are: difference between baseline (week 0) and week 36 in percent change in EASI from the baseline of the parent study (R668-AD-1334 or R668-AD-1416) for all randomized patients, and percent of patients with EASI-75 at week 36 for randomized patients with EASI-75 at baseline.

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). EASI accounts for both extent and severity of AD lesions and

has been designated as the preferred outcome measure for objective AD signs by expert consensus (Chalmers 2014). 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 scores (0-72) will be collected via the corresponding CRF page directly.

The percent change in EASI compared to baseline in parent study from baseline to Week 36 will be derived. Change in percent change in EASI from baseline over time will be derived as well.

A flag variable for denoting EASI-75 (≥75% improvement) at week 36 compared to the baseline EASI in the parent study (R668-AD-1334 or R668-AD-1416) will be derived.

The EASI will be collected at every scheduled and unscheduled clinic visit. For unscheduled clinic visit an analysis visit will be determined based on the analysis visit window described in Section 6.4.

4.4.2. Secondary Efficacy Variables

Key secondary endpoints are:

- Percent of patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with IGA(0,1) at baseline
- Percent of patients with IGA(0,1) at week 36 in the subset of patients with IGA(0,1) at baseline
- Percent of patients whose peak Pruritus NRS increased by 3 or more points from baseline to week 36 in the subset of patients with peak Pruritus NRS ≤7 at baseline

Other secondary endpoints (Unless otherwise specified, the analysis will be FAS for the following endpoints):

- Time to first IGA increase of ≥2 points from baseline in the subset of patients with IGA(0,1) at baseline
- Percent of patients with IGA scores 3 or 4 at week 36 in the subset of patients with IGA(0,1) at baseline
- Percent of patients with EASI-50 (≥50% reduction in EASI score from baseline of the parent study) through week 36
- Absolute change in EASI from baseline through week 36
- Absolute change in SCORAD score from baseline through week 36
- Absolute change in peak Pruritus NRS from baseline through week 36
- Absolute change in BSA from baseline through week 36

- Absolute change in POEM from baseline through week 36
- Absolute change in DLQI from baseline through week 36
- Absolute change in HADS from baseline through week 36
- Difference between baseline and timepoints through week 36 in percent change in SCORAD from the baseline of parent study
- Difference between current study baseline and timepoints through week 36 in percent change in Peak Pruritus NRS from the baseline of the parent study
- Annualized events rate of flares during the on-treatment period
- Proportion of well-controlled weeks during the on-treatment period
- Annualized event rate of skin infection TEAEs (excluding herpetic infections) during the on-treatment period

The following variables will be derived:

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.

Patients with IGA scores of 0 or 1 (clear or almost clear) at week 36 will be flagged. Change from the current study baseline over time will be derived. A flag variable for denoting IGA increase of ≥2 points from baseline at week 36 and IGA score 3 or 4 at week 36 will be derived, respectively.

EASI50

EASI-50 will be determined by visit through comparing with baseline in the parent study (R668-AD-1334 or R668-AD-1416). A flag variable for denoting the percent change reduction in EASI≥50% (EASI-50) at week 36 will be derived.

Peak Pruritus Numerical Rating Scale (NRS)

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

- For peak 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 were instructed on using the IVRS to record their Pruritus NRS score during the screening visit of their initial study. They will continue to be queried by site staff for compliance at each scheduled (and any unscheduled) clinic visit. Patients will complete the rating scale at time points according to Section 6.2 in the protocol.

If there are multiple NRS to the same question (peak itch intensity) collected on the same day, the worst score will be taken.

Change in weekly peak Pruritus NRS scores from baseline over time will be derived. A flag variable for denoting patients with an increase of ≥3 points in the weekly peak pruritus NRS at week 36 will be derived.

The percent change in weekly peak Pruritus NRS compared to baseline in parent study from baseline to Week 36 will be derived. Change in percent change in weekly peak Pruritus NRS from baseline over time will be derived as well.

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, which will be obtained through the CRF page directly. The maximum SCORAD score is 103.

Patients will undergo this assessment at every scheduled and unscheduled clinic visit.

Change in SCORAD from baseline over time will be derived.

The percent change in SCORAD compared to baseline in parent study from baseline to Week 36 will be derived. Change in percent change in SCORAD from baseline over time will be derived as well.

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:

1. 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.
2. If two or more questions are left unanswered the questionnaire is not scored.

3. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
4. 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.
5. If two or more response options are ticked for one question, the response option with the highest score should be recorded.
6. 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

Change in DLQI from baseline over time will be derived.

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 most appropriate responder definition for the POEM is a change score of 3.4 (Schram 2012), which equates to an individual patient change score of 4 points since the POEM is scored only in integers.

The POEM will be assessed at every scheduled and unscheduled clinic visit.

Change in POEM from baseline over time will be derived.

Hospital Anxiety and Depression Scale (HADS)

HADS is a validated, widely used questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions. Repeated administration also provides information about changes in a patient's emotional state (Bjelland 2002, Herrmann 1997, Zigmond 1983). The HADS questionnaire consists of 14 items that assess symptoms experienced in the previous week, with 7 items that are related to anxiety and 7 that are related to depression. Patients provided responses to each item based on a 4-point Likert scale. Each item on the questionnaire is scored from 0 (the best) to 3 (the worst); thus, 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 8 or more on the HADS-Anxiety or the HADS-Depression subscale were considered to be indicative of anxiety or depression, respectively (Bjelland 2002).

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. Change in HADS total from baseline over time will be derived.

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.

Change in BSA from baseline over time will be derived.

Proportion of patients with at least one skin infection TEAE (excluding herpetic infections) during on-treatment period

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.

A flag variable for denoting a patient with at least one skin infection during on-treatment period will be derived after adjudication by study medical monitor.

Time to first event (weeks) of an increase in IGA ≥2 compared to baseline (week 0) in the subset of patients with IGA(0,1) at baseline (week 0)

The time (weeks) from the baseline to the first an increasing in IGA≥2 compared to baseline will be calculated and a censoring variable will be derived and set to 0 if an increasing IGA≥2 observed regardless of the rescue medication use (See Appendix 10.5); otherwise, the time from baseline to the date of last visit will be calculated and the censoring variable will be set to 1.

Patients with flares

A flag variable regarding patients with flares will be derived by satisfying both of the following two conditions:

1. This patient received a rescue treatment determined by the algorithm in Appendix 10.5.
2. This patient whose latest EASI value or weekly peak Pruritus NRS prior to the rescue treatment administered got worse compared to baseline.

Proportion of well-controlled weeks during on-treatment period

During their weekly IVRS diary completion, patients will be asked: "Has your eczema been well-controlled over the last week?" Answer options will be "Yes" and "No." For the purpose of this protocol, well-controlled weeks are those for which patients answer "Yes" and during which no rescue treatments were administered.

The proportion of well-controlled weeks per patient will be derived based on the number of visits with responses prior to the rescue medication use divided by 37 planned visits during the on-treatment period.

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.).

As described in section 7.1.1 of the protocol, 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.

A Serious Adverse Event is an AE that is classified as serious according to the criteria specified in section 7.1.2 of the protocol. The information of AEs and SAEs will be collected through AE CRF page.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in section 7.2.5 of the protocol.

The observation period of AEs will be divided into three periods: pre-treatment, on-treatment, and overall study period:

- The pre-treatment period is defined as the period from the subject providing informed consent up to the first dose of study drug.
- The on-treatment period is defined as the period from day 1 to week 36 (day 253) or day of permanently withdraw from treatment, whenever earlier.
- Overall study period (on-treatment and follow-up period) is defined as the period from the administration of first study dose to the last study 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.

The severity of AEs will be graded as mild, moderate, or severe based on the criteria in section 7.3.1 of the protocol.

The relationship of AEs to study drug will be determined and categorized into two types: related and not related, by the investigator, and will be a clinical decision based on all available information.

For adverse events of special interest (AESI) there are two resources collecting them in this study: AE CRF page and the derived AESIs will be identified based on the criteria specified in the section 7.2.3 of the protocol. The searching criteria of AESI are listed in Appendix 10.4. The AESIs collected from these two resources will be reconciled.

4.5.2. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Clinical laboratory results (and units) including normal reference ranges and a flag variable denoting values outside the normal range (e.g. H or L) for continuous laboratory variables will be reported from the central laboratory and used in all summary tables. In addition, the change from baseline of the test results will be derived and used in summary tables as well. Baseline is defined as the test value used for analysis at week 16 in the initial studies, unless otherwise specified.

Some laboratory test values will also be programmatically flagged for an increase or decrease since baseline using the treatment emergent potentially clinically significant value (TEPCSV) criteria (see Appendix 10.3).

Blood samples for serum chemistry, hematology, and urinalysis testing will be collected at baseline (day 1), on days 85, 169, 253, and 337 (EOS) or ET, and at unscheduled visits. Pregnancy testing samples will be collected at baseline (day 1), very 4 weeks from baseline up to days 253, and day 337 (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. Tests will include:

Blood Chemistry

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

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

[2] CPK isoenzymes will be reflexively 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 (urine) for women of childbearing potential will be performed at time points according to Section 6.2 of the protocol.

Additional tests may be required to verify eligibility, or to clarify or help manage AEs. Any laboratory tests that are not specifically noted in the protocol require written approval from the medical monitor.

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 of the protocol.

4.5.3. Vital Sign, Weight, and Height Variables

The following parameters will be collected:

- Weight (kg) and height (cm)
- Respiratory rate (breath/min)
- Heart rate (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (°C)

Weight is determined on day 1/baseline, and days 253(week 36), 337 (week 48) (EOS), any unscheduled visits, or ET. Height is only measure at baseline (day 1). Other vital signs are collected at every scheduled and unscheduled clinic visit. If there are multiple measurements within the time window, the last value will be included.

Baseline is defined as the measurement used for analysis at week 16 in the initial studies.

The values of change from baseline will be derived by post-baseline visit for each of these parameters.

Vital sign and weight values satisfying the TEPCSV criteria (see Appendix 10.3) will be flagged.

4.5.4. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters provided by the ERT include: Ventricular HR, PR interval, QRS interval, RR interval, corrected QT interval (QTc Fridericia [QTcF] $=QT/[RR^{0.33}]$ and QTc Bazett [QTcB]$=QT/[RR^{0.5}]$). Overall interpretation for ECG status: normal and abnormal will also be collected. A standard 12-lead ECG will be performed at baseline, days 253 (week 36) and 337 (EOS), any unscheduled visits, or ET.

ECG parameters satisfying the TEPCSV criteria (see Appendix 10.3) will be flagged.

4.5.5. Physical Examination Variables

A physical examination will be conducted at baseline, and day 337 (EOS), any unscheduled visits, or ET. The result is an outcome of normal, abnormal not clinically significant, abnormal clinically significant or not examined. No derived variables are anticipated.

4.6. Pharmacokinetic (PK) Variables

Samples for measurement of functional dupilumab concentration in serum will be collected at visits described in schedule of events (Appendix 10.3). The following analyses will be provided in the clinical pharmacology sub-study report.

The pharmacokinetic profile of functional dupilumab in serum will be described graphically using the observed trough concentration data at the nominal times indicated. The impact of intrinsic factors (such as body weight, baseline EASI and race) on the trough concentration of dupilumab will be investigated graphically. If appropriate, pharmacokinetic variables may be reported including (but not limited to) $C_{last,}$ T_{max}, $T_{last,}$ time to steady state and $C_{troughSS}$ (steady state trough concentration).

In addition, the relationship between trough concentrations of dupilumab and the clinical response, as measured by EASI, IGA and Pruritus NRS will be explored graphically.

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 pre-existing immunoreactivity
  - Pre-existing immunoreactivity- defined as either an ADA positive response in the assay at baseline of the parent (SOLOs) study with all post first dose ADA results negative in the current study, OR a positive response at baseline of the parent (SOLOs) study with all post first dose ADA results in the current study less than 4-fold baseline titer levels of parent study.
- Total subjects with treatment-emergent response in the ADA assay
  - Treatment-emergent response is defined as a positive response in the ADA assay post first dose when baseline results in the parent (SOLOs) study are negative or missing.

The treatment-emergent response will be further characterized as:

  - 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 in the ADA assay
- Treatment-boosted response is 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 in the parent (SOLOs) study, when baseline results of the parent study are positive
- Titer Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

The baseline used to define ADA status (treatment-emergent, pre-existing immunoreactivity, etc.) refer to the baseline value in the parent (SOLOs) study.

ADA positive samples will be further characterized 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 IgEs for patients with a baseline level>LLQ only
- hs-CRP, ANA, anti dsDNA, anti-TPO

In addition to functioning as a safety marker, LDH has also been shown to correlate with AD disease severity/activity and suppressed by dupilumab. Thus, LDH (included in the clinical chemistry panel) will also be evaluated as a biomarker.

TARC and total serum IgEs 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 IgEs 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, Q1, Q3, 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 described in Section 4.1 will be summarized descriptively by treatment groups based on FAS and SAF, respectively.

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. Atopic and allergic disease history from SOLOs studies will be summarized in the same fashion as well.

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, 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 medications/procedures will be summarized by treatment group to MedDRA 18.0 at the time of BLA/MAA 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. In addition, prior medications and procedures ended prior to baseline will not be summarized in this study; only concomitant medications and procedures started prior to baseline and ended or ongoing after the first study treatment or started on or after baseline will be summarized.

Rescue medications/procedures will be summarized by treatment group by period (e.g. treatment period and follow-up period). The detailed information of rescue medications 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.

Listing of pre-treatment and concomitant medications/procedures will be provided. In addition, a listing of pre- treatment and concomitant medications for atopic dermatitis will be also provided.

The compliance of moisturizers (emollients) used will be summarized by treatment group.

5.4. Subject Disposition

The following summaries by table will be provided:

- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set and categorized by region
- The total number of patients with IGA(0,1) at baseline
- The total number of patients with EASI-75 responders at baseline
- The total number of patients who discontinued the study treatment and the reasons for treatment discontinuation
- The total number of patients who discontinued the study, and the reasons for study discontinuation and by visit
- Number of patients who entered into the follow-up period
- Number of patients who enrolled into an open-label extension study
- Number of protocol deviations will be summarized by treatment group. Protocol deviations will be categorized into major or minor protocol deviations. The number (n) and percentage (%) of patients with any protocol deviations, any major, and any minor protocol deviations will be summarized. If there are any major protocol deviations, the type of major protocol deviations will be presented as well.

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
- Listing of patients with protocol deviations will be provided

5.5. Dose Administration

The compliance with protocol-defined investigational product will be summarized by treatment group. It was defined as follows:

Treatment Compliance= (Number of injections during exposure period) / (Number of planned injections during exposure period) x 100%

Number of planned injections is determined based on the time period from the day 1 to the last non-rescue treatment visit administered.

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.

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:

≥ 28 days, ≥ 56 days, ≥ 84 days, ≥ 112 days, ≥ 140 days, ≥ 168 days, ≥ 196 days, ≥ 224 days, and ≥ 252 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. In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest is specified as:

≥28 days, ≥ 56 days, ≥ 84 days, ≥ 112 days, ≥ 140 days, ≥ 168 days, ≥ 196 days, ≥ 224 days, ≥ 252 days, ≥281 days and ≥337 days.

5.7. Analyses of Efficacy Variables

The following null and alternative hypotheses for the primary and key secondary endpoints will be tested for each of the dupilumab groups (300 mg qw or 300 mg q2w, 300 mg q4w, and 300 mg q8w) to the placebo group:

H0: $\text{Mean}_{\text{dupilumab}} = \text{Mean}_{\text{placebo}}$,

H1: $\text{Mean}_{\text{dupilumab}} \neq \text{Mean}_{\text{placebo}}$

The analyses of efficacy variables are described in the subsections below and summarized in Appendix 10.1.

Subgroups are defined by key baseline factors and listed to be considered for the comparisons between the dupilumab groups and placebo in primary and key secondary efficacy analyses:

- Age group (≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (no/yes)
- Race (White, Black, Asian and Other)
- History of duration of AD (< 26 years, ≥26 years) collected from parent studies
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)
- BMI (≥15-<30, ≥30-<50, ≥50)
- Region for global submission (Asia Pacific, Europe, and Americas)
- Region for Japan submission (Japan, Rest of world)- for Japan submission, only descriptive statistics is provided due to small number of patients in Japan
- Baseline median EASI (<median, ≥median)
- Previous use of systemic immunosuppressants for AD (Yes, No) prior to parent studies
- Previous use of systemic cyclosporine for AD (Yes, No) prior to parent studies
- Historical cyclosporine treatment subsets (subset 1: cyclosporine inadequate responders; subset 2: inadequately or intolerant to cyclosporine; subset 3: patients in subset 2 plus patients not received prior cyclosporine treatment) prior to parent studies
- Previous usage of Azathioprine (Aza) (Yes, No) prior to parent studies
- Previous usage of Methotrexate (MTX) (Yes, No) prior to parent studies
- Baseline body surface area (BSA) (≤10%, >10%)
- History of asthma (Yes, No) collected from parent studies
- History of allergic rhinitis (Yes, No) collected from parent studies
- History of food allergies (Yes, No) collected from parent studies

Graphic plots (e.g. forest plots) for the comparisons between the individual and combined dupilumab treatment groups and placebo regarding these key baseline factors may be provided.

5.7.1. Analysis of Primary Efficacy Variables

Continuous primary efficacy variable: Difference in percent change in EASI compared to the baseline in R668-AD-1334 or R668-AD-1416 between baseline and week 36 will be analyzed in FAS by using the multiple imputation (MI) with analysis of covariance (ANCOVA) model.

Patients' efficacy data through week 36 after the rescue medication usage or early discontinuation will be set to missing first, and then be imputed by the multiple imputation

method. Missing data will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure. 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, treatment regimen in the parent studies, randomization strata (disease severity), and current study baseline.

Each of the 40 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment, treatment regimen in the parent studies, randomization strata (disease severity: baseline IGA=0 vs 1 vs >1, and region: Americas, Europe, and Asia Pacific including Japan), and current study baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, treatment regimen in the parent studies, current study baseline value and the randomization strata
- Measured endpoint values from every clinic visit up to week 36

Randomization strata in the efficacy analyses will be based on the data collected by the interactive voice response system (IVRS) at randomization (as randomized).

Graphs of least-square means ±SE by visit for percent change from baseline will be presented.

Sensitivity analyses for the continuous variable

In addition to the MI method described above, sensitivity analyses for the primary endpoint will be conducted as described below:

1. A sensitivity analysis will use ANCOVA model as described above based on all observed data no matter if rescue medication is used
2. A sensitivity analysis will use a mixed-effect model repeated measures (MMRM). The model will include factors (fixed effects): treatment group, treatment regimen in parent studies, randomization strata (disease severity: baseline IGA=0 vs 1 vs >1, and region: Americas, Europe, and Asia Pacific including Japan), visit, current study 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 36 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. A sensitivity analysis will use ANCOVA model, including the treatment group, treatment regimen in parent studies, current study 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. A sensitivity analysis will use ANCOVA model, including the treatment group, treatment regimen in parent studies, current study 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.

Categorical primary efficacy variable: percent of patients with EASI-75 at week 36 it will be analyzed in the subset of patients with EASI-75 at baseline by a Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (disease severity: baseline IGA=0 vs 1 vs >1, region: Americas, Europe, and Asia Pacific including Japan.), and treatment regimen in parent studies. This analysis may also be performed in FAS.

Handling of dropouts or adjudicated rescue medication or missing value for the categorical response variables in the primary analysis

If a patient receives any rescue medications (see Section 4.3 for rescue medications) prior to week 36 or withdraws from the study, this patient will be counted as a non-responder from the time of the use of rescue treatment or withdrawal.

Sensitivity analyses for the categorical variable

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 36 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). No imputation will be conducted.

The primary efficacy analyses will be performed in FAS for continuous efficacy variable and the subset of patients with EASI-75 at baseline for categorical efficacy variable, as well as on PPS as a supporting analysis. Plots of the primary variables over time will be presented.

5.7.2. Analyses of Key Secondary Efficacy Variables

For the key secondary efficacy endpoints described in Section 4.4.2 the categorical efficacy endpoints will be analyzed using the same approach as those used for the analysis of the primary endpoints.

5.7.3. Multiplicity Considerations

For the comparisons of dupilumab treatment groups vs placebo, a hierarchical two-sided testing procedure with an alpha level of 0.05 will be adopted for the primary and key secondary efficacy endpoints in a pre-specified order as follows:

1. Difference (from baseline (week 0) to week 36) in percent change in EASI compared to the baseline in R668-AD-1334 or R668-AD-1416
2. Percent of patients with EASI-75 at week 36
3. Percent of patients whose IGA response at week 36 was maintained within 1 point of baseline (week 0)
4. Percent of patients with IGA scores 0 or 1 at week 36
5. Percent of patients with peak pruritus NR increase by ≥3 points from baseline (week 0) to week 36

If an endpoint is significant at a 2-sided 0.05 level, the sequential analysis will continue for the next endpoint until the significance level is no longer met.

If all tests are significant from the primary to key secondary endpoints, the same hierarchical testing procedure will apply to dupilumab 300 mg q4w vs. placebo and then dupilumab 300 mg q8w vs. placebo. The testing order will be as follows:

1. High dose group (300 mg qw or q2w) vs placebo: in the order of items 1-5 above; then
2. Middle dose group (300 mg q4w) vs placebo: in the order of items 1-5 above; then
3. Low dose group (300 mg q8w) vs placebo: in the order of items 1-5 above

5.7.4. Subgroup Analysis

Subgroups described in Section 5.7 for the primary (co-primary) endpoint and key secondary efficacy endpoints listed in Section 5.7.1 and Section 5.7.2 will be analyzed. The analysis method for the subgroup analysis will be conducted using the primary analysis of category and continuous endpoints described in Section 5.7.1. Interactions between the subgroups and treatment groups will also be tested.

Forest plots of the primary (co-primary) and key secondary efficacy endpoints across subgroups will be generated.

5.7.5. Analyses of Other Secondary and Exploratory Efficacy Variables

For categorical and continuous variables they will be analyzed using the same approaches as those used for the analyses of the primary endpoints without performing sensitivity analyses.

Percent of patients with IGA scores 3 or 4 at week 36

For this endpoint if a patient has the missing value at week 36 or received any rescue treatment prior to week 36, then this patient will be counted as an IGA(3,4) responder at week 36.

Analysis of time-to-event endpoints

For time-to-event endpoint described in Section 4.4.2 (e.g. Time to first IGA increase of ≥2 points from baseline) the stratified log rank test will be performed by considering the randomization strata. The quartile estimates along with 95% confidence intervals for treatment groups and hazard ratio will be presented. The Kaplan-Meier curves will be provided for regimen groups.

Analysis of incidence of TEAE-related variables

1. Annualized event rate of skin infection TEAEs (excluding herpetic infections) during on-treatment period
2. Annualized events rate of flares during the on-treatment period

These endpoints will be analyzed for patient in SAF.

For items above a negative binomial regression model with number of events as response variable and treatment and randomization strata (disease severity) as covariates will be used for estimating the mean rate adjusted by the on-treatment duration on log scale through the offset option in SAS PROC GENMOD procedure. Relative risk between treatment groups and placebo will be performed along with 95% confidence intervals.

5.8. Analysis of Safety Data

The summary of safety and tolerability 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)
- 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 on-treatment period, and overall study period, described in Section 4.5.1. Adverse event (AE) incidence tables will be presented for each dose regimen along with total of dupilumab doses as well as for selected subgroups (Section 5.8), 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. 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
- Date of first study treatment administered
- 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, Unknown, Not applicable, and other, specify
- 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-Years (NEP100Y) and Number of Patients with at least one event per 100 Patient-Years (NPP100Y). These

calculations will be adjusted for dose exposure for the on-treatment period and for the entire study period. The 100 Patient-Years for events and patients will be applied to AESIs and SAEs.

Number of events per 100 patient-years (NEP100Y)

The NEP100Y 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.

$$\text{NEP100Y} = 100 \times \frac{\sum n_i}{\sum T_i}$$

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 (NPP100Y)

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 (365.25 days). The number of patients with at least one event per 100 patient-years will be calculated as the number of patients at risk of an initial occurrence of the event having a specific event divided by the total person-year. In particular, the EAIR is computed as follows:

$$\text{EAIR} = 100 \times \frac{n}{\sum t_i}$$

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.

Time to first AESIs (TEAE by category) and time to TEAE leading to permanent treatment discontinuation during the on-treatment period

These time-to-event endpoints will be assessed by Kaplan-Meier estimates (K-M plot). The time is defined as the date of first event – the date of first dose + 1 during the 36-week treatment period if an event was observed or defined as the date of last visit – the date of first dose + 1 during the 36-week treatment period if there was no any event.

In order to detect any safety signals, the hazard ratio (HR) will be provided along with the corresponding 95% confidence interval (CI) for the adverse events>=1% in any regimen group during the 36 week treatment period. Hazard ratios will be calculated using a Cox regression model including factors of treatment group, and randomization strata. 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
- Serious TEAE

- TEAE leading to death
- TEAE leading to permanent treatment discontinuation
- TEAEs leading to temporary treatment discontinuation
- TEAE by maximum intensity (mild, moderate, severe)

Adverse event of special interest (AESI) by syndrome:

- Anaphylactic reactions
- Acute allergic reactions that require treatment
- Severe injection site reactions 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
- Any infection requiring treatment with oral antibiotics/anti-viral/anti-fungal for
- longer than 2 weeks
- Any clinical helminth endoparasitosis
- Any opportunistic infection
- Suicidal behavior (suicidal ideation, suicidal behavior, depression suicidal, suicide attempt and completed suicide)
- Conjunctivitis based on narrow CMQ (Narrow Conjunctivitis)
- Conjunctivitis based on broad CMQ (Broad Conjunctivitis)

Appendix 10.5 provides a list of AESIs search criteria.

Number and proportions of patients reporting TEAEs will be summarized as follows:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - TEAEs related to study medication by SOC/PT
  - Severe TEAEs related to study medication by SOC/PT
  - TEAEs leading to permanent treatment discontinuation by SOC/PT
  - TEAEs leading to temporary treatment discontinuation by SOC/PT

  - TEAEs of special interest derived from the programming algorithm by AESI category and by HLT/PT
  - TEAEs of special interest collected by AE CRF page by HLT/PT
  - TEAEs by ≥5% of patients in any dose regimen by SOC/PT
  - TEAEs by ≥5% of patients in any dose regimen by SOC/HLT/PT
- Serious TEAEs
  - Serious TEAEs by SOC/PT
  - Serious TEAEs related to study medication by SOC/PT
- TEAEs result in death by SOC/PT
- Injection site reaction events by PT
- Injection site reaction events by SOC/HLT/PT
- Herpes infection events by PT
- Skin infection events by PT
- Skin infection events by SOC/HLT/PT

Summaries of TEAEs will also include:

- Number of events for each corresponding table
- Number and proportion of subjects with at least one TEAE for each corresponding table

The summaries will also be presented by key baseline factors described in Section 5.8.

Number of patients with exposure-adjusted TEAEs per 100 patient-years and Number of TEAEs per 100 patient-years

Number and proportion of patients with TEAE per 100 patient-years and number of TEAEs per 100 patient-years will be summarized in the on-treatment period and the overall period.

- TEAEs by SOC and PT
- Severe TEAEs by SOC/PT
- TEAEs related to study medication by SOC/PT
- Severe TEAEs related to study medication by SOC/PT
- Serious TEAEs by SOC/PT
- Serious TEAEs related to study medication 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
- TEAEs of special interest derived from the programming algorithm by AESI category and by HLT/PT

- Number of patients with TEAEs per 100 patient-years ≥5% of patients in any dose regimen by SOC/PT
- Number of patients with TEAEs per 100 patient-years ≥5% of patients in any dose regimen by SOC/HLT/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.

TEAEs/SAEs/AESI during on-treatment period and overall period will be listed. Death, TEAEs leading to treatment discontinuation, and skin infection TEAEs will be listed as well.

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 results and change from current study baseline by visit
- The number (n) and percentage (%) of subjects with abnormal lab value during study whose baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs during study
- Shift tables based on current study 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. Graphs of mean change (±SE) from baseline in laboratory parameters by visit during on-treatment period will be presented. Also, a figure of peak ALT vs peak total bilirubin (TBL) on log scale along with reference lines for 3xULN for ALT and 2xULN for TBL will be presented for detecting patients with potentially serious liver injury.

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
- 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. Graphs of mean change (±SE) from baseline by visit during on-treatment period will be presented.

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 over time
- 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, 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 patients.

The following summaries will be performed on the AAS:

- Number (%) of patients with ADA status (negative or positive in the ADA assay) at time points analyzed 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
- ADA peak titers using descriptive statistics (median, minimum and maximum) for pre-existing immunoreactivity, treatment-emergent, treatment-boosted ADA response by treatment group

- ADA titers using descriptive statistics (median, minimum and maximum) by treatment group and at each ADA time point analyzed
- Number (%) of patients with NAb status (negative or positive in the NAb assay) by treatment group

Association between ADA variables (e.g. ADA peak titers, neutralizing antibody status, treatment-emergent, treatment-boosted, transient, indeterminate and persistent ADA responses) and functional dupilumab concentrations may be explored. Individual dupilumab concentrations may be assessed by presenting the functional dupilumab concentrations over time by ADA/NAb status and by maximum titer category (scatter plots and spaghetti plots). These assessments of ADA and associated changes in longitudinal drug concentrations, or PD (defined as any potential drug induced biological response) may be provided in the clinical pharmacology sub-study 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]) confirmed by manual adjudication
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Number (%) of patients with the above mentioned safety events will be summarized by ADA status (positive or negative), and neutralizing antibody (positive or negative) status during the TEAE period.

In addition, the primary endpoint and key secondary efficacy endpoints may be summarized in patients with and without ADA (positive vs. negative) and neutralizing antibody (positive or negative) status if applicable. The effect of ADA/NAb status on both dupilumab concentrations and on the clinical response may be assessed by plotting and comparing the mean functional dupilumab concentration and the mean % change from baseline in clinical response by ADA and NAb status and provided in the clinical pharmacology sub-study report.

5.11. Analysis of Biomarkers

Descriptive statistics for the observed values, change and percent change from baseline (week 0) by treatment and visit will be provided for the following biomarker variables at baseline, days 85,169, 253, and 337:

- TARC
- total serum IgE
- antigen-specific IgE
- hs-CRP

Proportions for the following binary biomarkers will be reported:

- ANA, anti dsDNA, anti-TPO

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 10 (week 36). After visit 10, no imputation will be made. P-value for difference from placebo will be provided.

The relationship of flare and biomarker in a time interval is explored. For each time interval of ≥1 - 85, ≥85-169, ≥ 169-253, ≥253-337 and 337+ day, associations of change / percent change from baseline in TARC, total serum IgE, and antigen-specific IgE separately and the flare will be explored per regimen group and combined dupilumab regimen groups using the ANOVA/ANCOVA model. For the time interval of [1, 85), each baseline values of TARC, total serum IgE, and antigen-specific IgE is the dependent variables and status of flare (Y/N) in interval [1,85) is the independent variable in the ANOVA model respectively. For the time interval other than [1, 85), say (≥Day X-Day Y). Change/percent change in each of TARC, total serum IgE, and antigen-specific IgE from baseline to Day X is the dependent variable, and baseline and status of flare in interval (≥Day X – Day Y) are the independent variables in the ANCOVA model. P-value will be provided to show significance of the flare effect on dependent variable.

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. In addition, the same fashion will apply to two subgroups based on the treatment regimens (300 mg QW and 300 mg Q2W) received in SOLOs studies. The standard line plots (means +/- se) for continuous variables will be provided.

All above analyses will be performed in 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.

5.11.1. Normalization Analyses

The additional analyses to be performed are to evaluate the proportion of patients for whom biomarker concentrations “normalize” (shift from above normal to within the normal range compared to the parent study baseline) at week 36. The additional analysis will be performed on the following biomarkers:

- Total IgE
- Allergen specific IgEs

- TARC

Method for Determining a ULN for Total IgE and Allergen-specific IgEs

Total IgE and the allergen-specific IgEs are established clinical assays; the upper limit of normal (ULN) from the central lab reference range will determine the threshold for normal vs. elevated status.

The reference ranges for the total IgE (Phadia 2015) and allergen-specific IgEs (Phadia 2014) are specified in Table 1, from the product inserts provided by the manufacturer of the assays.

Table 1: Reference Range of Total IgE and Allergen-Specific IgEs

Allergen (Analyte)	Phadia Code	Catalog #	Reference Range
Allergen Total IgE		14-4509-01	0-119 kU/L for both adult sexes
Allergen specific IgE Dermatophagoides pteronyssinus, d1	d1	14-4107-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Cat Dander, e1	e1	14-4109-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Mold Mix 1	mx1	14-4204-01	negative
Allergen specific IgE Olive Tree	t9	14-4150-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Tree Mix 1	tx1	14-4199-01	negative
Allergen specific IgE Mountain juniper	t6	14-4225-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Grass Mix 2	gx2	14-4192-01	negative
Allergen specific IgE Wall Pellitory (Parietaria officinalis)	w19	14-4186-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Candida albicans	m5	14-4120-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Pityrosporum (Malassezia)	m70	14-4349-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Dermatophagoides farinae	d2	14-4108-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Grass Mix 1	gx1	14-4163-01	negative
Allergen specific IgE Weed Mix 2	wx2	14-4268-01	negative
Allergen specific IgE Japanese Cedar, t17	t17	14-4118-01	<0.35 kU/L for both sexes and all ages
Allergen specific Oak (Quercus alba)	t7	14-4149-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Staphylococcal enterotoxin A	m80	14-4889-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Staphylococcal enterotoxin B	m81	14-4890-01	<0.35 kU/L for both sexes and all ages

Allergen (Analyte)	Phadia Code	Catalog #	Reference Range
Allergen specific IgE Egg white	f1	14-4111-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Cow's milk	f2	14-4112-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Peanut	f13	14-4112-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Soybean	f14	14-4115-01	<0.35 kU/L for both sexes and all ages
Allergen specific IgE Wheat	f4	14-4113-01	<0.35 kU/L for both sexes and all ages

Method for Determining a ULN for TARC

A standard reference range for TARC in healthy adult populations has not been established. To determine an appropriate ULN for these analyses, a literature review was conducted to identify summary estimates of TARC in healthy adult volunteers, in studies using identical methodology (ELISA, R&D Systems, Minneapolis) to measure serum TARC levels (pg/mL). Two comparable studies were identified and estimates are provided in Table 2. Along with these estimates, data from a FIH Study (R668-AS-0907) was included to supplement available information and ensure consistency across internally and externally obtained measurements of serum TARC. The R668-AS-0907 study comprised healthy volunteers and the TARC measurements provided in Table 2 were obtained at Day 1, prior to administration of study drug or placebo.

From the two external and one internal estimates, a combined mean and SD were calculated (using the study healthy volunteers sample size as weights). The mean combined serum TARC level + two standard deviations was used to determine the ULN. After combining data across studies, the calculated ULN for serum TARC is 1081.5 pg/mL. Under the assumption that serum TARC levels are normally distributed in healthy adults, approximately 95 percent of normal serum TARC levels will fall within this range. From the summary data identified by literature review, as well as our internal data, serum TARC levels in healthy adults appear to have a slight right skew. However, for the purposes of this analysis, the normal distribution assumption should provide a more conservative estimate of the ULN (in comparison to using 95th percentile or maximum study measurements), thereby increasing the burden of establishing normalization of serum TARC levels in our patient population. Additionally, from internal study R668-AS-0907, the 90 - 95 percentile for TARC at Day 1 was 1042 – 1142 pg/mL, consistent with the calculated ULN (percentile information from external sources was not available).

Table 2: External/Internal Reference Estimates of TARC

Sample Type	Detection Method	Healthy Controls			Reference
		Sample Size	Mean	Standard Deviation	
Serum	ELISA (R&D, Minneapolis USA)	48	616	290.6	Internal REGN Study: R668-AS-0907
Serum	ELISA (R&D, Minneapolis USA)	44	437.9	292	K. Jahnz-Rozyk, et al,"Serum thymus and activation-regulated chemokine, macrophage derived chemokine and eotaxin as markers of severity of atopic dermatitis." Allergy 2005: 60: 685–688
Serum	ELISA (R&D, Minneapolis USA)	20	258	123	Caproni M, et al; "Serological detection of eotaxin, IL-4, IL-13, IFN-g,MIP-1a, TARC and IP-10 in chronic autoimmune urticaria and chronic idiopathic urticaria." J Dermatol. Science (2004) 36, 57-59
	COMBINED:	**112**	**482.1**	**299.7**	**ULN: 1081.5 (482.1+2*299.7)**

5.11.2. Normalization Biomarker Data Related Evaluations

Patients in the subset of FAS populations are specifically defined as below:

- Include the elevated total IgE, allergen-specific IgE, or TARC at Baseline in the "normalization" analyses, respectively, for the biomarkers for which their Baseline serum levels are elevated. Patients in FAS with a normal (below the ULN) serum biomarker level at Baseline will be excluded from the analysis for that biomarker, and
- At least one post-baseline measurement and received treatment.

Therefore, the analysis population for each of the biomarkers of interest will vary depending on the number of FAS patients meeting "elevation" criteria at baseline.

The last observation carried forward (LOCF) approach will be used to impute missing total IgE, allergen-specific IgEs and TARC data for visits between post-baseline and Week 36. After Week 36, no imputation will be made. Patients who received rescue medications will have all subsequent measurements set to missing and the last observation prior to first use of rescue medication will be used for the LOCF approach.

To further evaluate the main analysis results, a sensitivity analysis will be conducted. The observed biomarker values at week 36 will be used in this analysis (denoted as OC), regardless of whether a patient dropped out of the study or used rescue medication prior to week 36.

Summary tables with normal/elevated status for total IgE, allergen-specific IgEs, and TARC at baseline and each post-baseline visit (until end-of-study) will be provided by treatment group.

For the biomarkers with at least 5 evaluable patients in both the dupilumab and placebo treatment groups at Week 36, a Cochran-Mantel-Haenszel test will be conducted to compare the

proportion of patients achieving normalized status across treatment groups, stratified by randomization strata (region, disease severity), for both the LOCF and sensitivity (OC) analysis approaches. The test statistic p-values for the comparison of the dupilumab groups versus placebo and point estimate with 95% confidence interval will be provided.

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 measurement used for analysis at week 16 in the initial studies.

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 signs, 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	Baseline	1	1
2	Week 4	29	[2,43]
3	Week 8	57	[44, 71]
4	Week 12	85	[72,99]
5	Week 16	113	[100,127]
6	Week 20	141	[128,155]
7	Week 24	169	[156,183]

8	Week 28	197	[184,211]
9	Week 32	225	[212,239]
10	Week 36 (EOT)	253	[240,267]
11	Week 40	281	[268,309]
12	Week 48 (EOS)	337	>=310

* 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 weekly via IVRS, the analysis visit windows will be as follows:

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days
1	Baseline	1	1
2	Week 1	8	[2,11]
3	Week 2	15	[12,18]
4	Week 3	22	[19, 25]
5	Week 4	29	[26, 32]
6	Week 5	36	[33, 39]
7	Week 6	43	[40, 46]
8	Week7	50	[47, 53]
9	Week 8	57	[54, 60]
10	Week 9	64	[61, 67]

11	Week 10	71	[68, 74]
12	Week 11	78	[75, 81]
13	Week 12	85	[82, 88]
14	Week 13	92	[89, 95]
15	Week 14	99	[96, 102]
16	Week 15	106	[103, 109]
17	Week 16	113	[110, 116]
18	Week 17	120	[117, 123]
19	Week 18	127	[124, 130]
20	Week 19	134	[131, 137]
21	Week 20	141	[138, 144]
22	Week 21	148	[145, 151]
23	Week 22	155	[152, 158]
24	Week 23	162	[159, 165]
25	Week 24	169	[166, 172]
26	Week 25	176	[173, 179]
27	Week 26	183	[180, 186]
28	Week 27	190	[187, 193]
29	Week 28	197	[194, 200]
30	Week 29	204	[201, 207]
31	Week 30	211	[208, 214]
32	Week 31	218	[215, 221]
33	Week 32	225	[222, 228]
34	Week 33	232	[229, 235]
35	Week 34	239	[236, 242]
36	Week 35	246	[243, 249]
37	Week 36	253	[250, 256]
38	Week 37	260	[257, 263]
39	Week 38	267	[264, 270]
40	Week 39	274	[271, 277]
41	Week 40	281	[278, 284]

42	Week 41	288	[285, 291]
43	Week 42	295	[292, 298]
44	Week 43	302	[299, 305]
45	Week 44	309	[306, 312]
46	Week 45	316	[313, 319]
47	Week 46	323	[320, 326]
48	Week 47	330	[327, 333]
49	Week 48	337	≥334

7. INTERIM ANALYSIS

No interim analysis is to be performed.

8. SOFTWARE

All analyses will be done using SAS Version 9.2 or above.

9. REFERENCES

Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. Br J Dermatol 1999;141:698-702.

Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the Minimal Clinically Important Difference and Responsiveness of the Dermatology Life Quality Index (DLQI): Further Data. Dermatology. 2015;230(1):27-33.

Bjelland I, Dahl AA, Haug TT et al. Review: The validity of the hospital anxiety and depression scale, an updated literature review. J Psychosom Res 2002;52:69-77.

Chalmers JR, Schmitt J, Apfelbacher C, Dohil M, Eichenfield LF, Simpson EL, Singh J, Spuls P, Thomas KS, Admani S, Aoki V, Ardeleanu M, Barbarot S, Berger T, Bergman JN, Block J, Borok N, Burton T, Chamlin SL, Deckert S, DeKlotz CC, Graff LB, Hanifin JM, Hebert AA, Humphreys R, Katoh N, Kisa RM, Margolis DJ, Merhand S, Minnillo R, Mizutani H, Nankervis H, Ohya Y, Rodgers P, Schram ME, Stalder JF, Svensson A, Takaoka R, Teper A, Tom WL, von Kobyletzki L, Weisshaar E, Zelt S, Williams HC. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). Br J Dermatol. 2014 Dec;171(6):1318-25. doi: 10.1111/bjd.13237. Epub 2014 Nov 14.

Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol 2004;140:1513-1519.

Hanifin JM, Thurston M, Omoto M et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001;10: 11-18.

Herrmann C. International Experiences with the Hospital Anxiety and Depression Scale – A Review of Validation Data and Clinical Results; Journal of Psychosomatic Research, Vol. 42, No. 1, pp 17-41, 1997

ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

No authors listed. Severity scoring of atopic dermatitis: the SCORAD index: consensus report of the European task force on atopic dermatitis. Dermatology 1993;186: 23-31.

Phadia AB, 2014-Apr-24: ImmunoCAP® Total IgE Fluoroenzyme immunoassay, CLIA Complexity Category = Moderately Complex, Directions for Use 52-5292-US/01

Phadia AB, 2015-Jan-9: ImmunoCAP® Specific IgE Conjugate 100 and 400, Fluoroenzyme immunoassay CLIA Complexity Category = Moderately Complex, CLIA Complexity Category = Moderately Complex, Directions for Use 52-5256-02/17, Calibrator range 0-100 kU/l

Schram ME, Spuls PI, Leeflang MMG, et al. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67:99–106.

Winthrop KL, Novosad SA, Baddley JW,et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015;74:2107–2116.

Zigmond AS, Snaith RP: The Hospital Anxiety And Depression Scale. Acta Psychiatr Scand 1983, 67:361-70.

10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Primary continuous variable: Difference of percent change in EASI from current study baseline to week 36	FAS	ANCOVA with MI	MMRM, ANCOVA with MI on OC, WOCF and LOCF, and on PPS	Yes	Line Plot, Forest plot
Primary categorical variable: percent of patients with EASI-75 at week 36	EASI-75 at baseline in FAS	Cochran-Mantel-Haenszel test stratified by IGA status and region at randomization, and treatment regimen in parent studies.	LOCF after censoring for rescue treatment use, LOCF on OC regardless rescue treatment use, and OC	Yes.	Line Plot, Forest plot
Key Secondary categorical variables	FAS, NRS≤7 at baseline in FAS	Cochran-Mantel-Haenszel test stratified by IGA status and region at randomization, and treatment regimen I parent studies.	LOCF after censoring for rescue treatment use, LOCF on OC regardless rescue treatment use, and OC	Yes	Line Plot, Forest plot
Other Secondary continuous variables	FAS	ANCOVA with MI, MMRM		No	Line plot
Other Secondary categorical variables	FAS, IGA(0,1) at baseline in FAS	Cochran-Mantel-Haenszel test stratified by IGA status and region at randomization, and treatment regimen I parent studies.		No	Line plot
Event rate variables	SAF	Negative binomial regression,		No	

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	Yes	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	**Treatment Period**										**Follow-up**		
Visit (V)	**Baseline V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**Primary Endpoint Visit V 10**	**V 11**	**End of Study V 12**	**Early Termination or Unscheduled Visit[4]**
Week (W)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W48**	
Day (D) Visit Window (d)	**D1[1]** **+/-3d**	**D29** **+/-3d**	**D57** **+/-3d**	**D85** **+/-3d**	**D113** **+/-3d**	**D141** **+/-3d**	**D169** **+/-3d**	**D197** **+/-3d**	**D225** **+/-3d**	**D253** **+/-3d**	**D281** **+/-7d**	**D337** **+/-7d**	
Screening/Baseline:													
Inclusion/Exclusion	X												
Informed Consent	X												
Demographics	X												
Concurrent illnesses	X												
Randomization	X												
Training on IVRS[2]	X[3]												
Treatment:													
Study drug dispensation[4]	X	X	X	X	X	X	X	X	X				
Study drug accountability		X	X	X	X	X	X	X	X	X			
Study drug administration[4]	X	Dupilumab or placebo, depending on treatment arm, through week 35											
Patient dosing diary[5]		X	X	X	X	X	X	X	X	X			
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy: [6]													
Pruritus NRS and Categorical Scale [7]	X	Weekly by patient diary, through the end of the study											
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	**Treatment Period**										**Follow-up**		
Visit (V)	**Baseline V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**Primary Endpoint Visit V 10**	**V 11**	**End of Study V 12**	**Early Termination or Unscheduled Visit[4]**
Week (W)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W48**	
Day (D) Visit Window (d)	**D1[1]** **+/-3d**	**D29** **+/-3d**	**D57** **+/-3d**	**D85** **+/-3d**	**D113** **+/-3d**	**D141** **+/-3d**	**D169** **+/-3d**	**D197** **+/-3d**	**D225** **+/-3d**	**D253** **+/-3d**	**D281** **+/-7d**	**D337** **+/-7d**	
POEM, DLQI, EQ-5D, HADS[8]	X			X			X			X		X	X
Patient Global Assessment of Disease	X			X			X			X		X	X
Patient Global Assessment of Treatment	X			X			X			X		X	X
ACQ-5, SNOT-22[8]	X									X		X	X
Well-controlled weeks (weekly diary)	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess sick leave/missed school days	X	X	X	X	X	X	X	X	X	X	X	X	X
Photograph AD area (select sites)[9]	X									X		X	X
Safety: [10]													
Weight	X									X		X	X
Height	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X											X	X
Electrocardiogram	X									X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[10]:													
Hematology	X			X			X			X		X	X

Study Procedure	**Treatment Period**										**Follow-up**		
Visit (V)	**Baseline V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**Primary Endpoint Visit V 10**	**V 11**	**End of Study V 12**	**Early Termination or Unscheduled Visit[4]**
Week (W)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W48**	
Day (D) Visit Window (d)	**D1[1]** **+/-3d**	**D29** **+/-3d**	**D57** **+/-3d**	**D85** **+/-3d**	**D113** **+/-3d**	**D141** **+/-3d**	**D169** **+/-3d**	**D197** **+/-3d**	**D225** **+/-3d**	**D253** **+/-3d**	**D281** **+/-7d**	**D337** **+/-7d**	
Chemistry	X			X			X			X		X	X
Urinalysis	X			X			X			X		X	X
Urine Pregnancy Test (WOCBP only) [11]	X	X	X	X	X	X	X	X	X	X		X	X
TARC	X			X			X			X		X	X
Total serum IgE	X			X			X			X		X	X
Antigen-specific IgE samples	X			X			X			X		X	X
Hs-CRP, ANA, anti-dsDNA, anti-TPO	X			X			X			X		X	X
Skin microbiome samples[12]	X			X			X			X		X	X
Research samples (serum/plasma)	X			X			X			X		X	X
PK/Drug Concentration and ADA Samples[10]:													
Functional dupilumab PK sample	X	X		X			X			X		X	X
Anti-dupilumab antibody sample[13]	X	X		X			X			X		X	X

1. All day 1 procedures overlap with procedures and assessments performed at week 16 in the parent studies, and should be performed only once, with the exceptions of the informed consent procedure, IVRS training, measurement of height, and administration of study drug.
2. Patients will be trained to use the appropriate diary system to report pruritus and provide other information as required (eg, well-controlled weeks).
3. Patients will begin using the diary system at week 1.

4. At each study visit from day 1 through week 32, patients will be provided with a 4-week supply of study drug for administration outside the study site. The first injection will be administered at the study site. Patients will return the original kit boxes at each clinic visit. Study drug may also be dispensed during an unscheduled visit, if necessary.
5. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and any related issues; counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside the clinic.
6. Assessments/procedures should be conducted in the following order: patient reported outcomes, investigator assessments, safety and laboratory assessments, administration of study drug.
7. Patients will start calling the appropriate diary system at week 1.
8. 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). Asthma Control Questionnaire (ACQ-5) will be administered only to patients with a medical history of asthma. Sinonasal Outcome Test -22 (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.).
9. Select sites only – photograph AD area.
10. To be collected before the injection of study drug. Patients should be instructed to fast for 6 to 8 hours before blood sample collection. However, blood samples will be collected even if patients report to the study site without fasting. The status of the sample ("fasting" or "non-fasting") should be noted in the laboratory records.
11. A negative urine pregnancy test result is required before administration of study drug.
12. Noninvasive skin swabs; this may be performed at select sites only.
13. Patients who are ADA positive at their last study visit (early termination or end of study visit), and who do not participate in the open-label extension study, will be considered for follow-up based on their overall presentation at that time.

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 Internal DILI WG Oct 2008 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. Internal DILI WG Oct 2008 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. Internal DILI WG Oct 2008
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 2008 Internal DILI WG Oct 2008 * 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	<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 Additional: ≥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. Search Criteria for TEAE of Special Interest/TEAE Syndrome

AESI	Atopic Dermatitis
Anaphylactic reaction	Anaphylactic reaction narrow SMQ (20000021)
Acute allergic reactions that require treatment	Hypersensitivity narrow SMQ (20000214); then refine based on - Medication given for TEAE as recorded on ConMed CRF page - *Blinded manual adjudication of relevant PTs by the study medical monitor before database lock*
Severe Injection Site Reaction that has last longer than 24 hours	HLT = 'Injection site reaction' and Intensity='Severe'
Mycosis fungoides or other forms of cutaneous T cell lymphoma	HLT = 'Mycosis fungoides'; includes LLT = Sezary syndrome and LLT = Cutaneous T-cell lymphoma PT = 'Cutaneous T-cell dyscrasia'
Any severe Infection	Primary SOC = 'Infections and infestations' and Intensity='Severe'
Any infection requiring treatment with parenteral antibiotics	Primary SOC = 'Infections and infestations' and ConMed: ATC1= "Antiinfectives for systemic use" 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 = 'Infections and infestations' and Check CM: ATC1= "Antiinfectives for systemic use" during the TEAE course (between start and stop dates), Route = PO and Treatment duration >14 days
Any clinical endoparasitosis	HLTs of • 'Cestode infections' • 'Helminthic infections NEC' • 'Nematode infections' • 'Trematode infection'
Any opportunistic infection (Winthrop 2015)	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

AESI	Atopic Dermatitis
	-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: *For items noted with the asterisk, blinded manual adjudication of relevant PTs will be required by the study medical monitor, before database locks*
Suicidal behavior	PTs of • Completed suicide • Suicidal ideation • Depression suicidal • Suicidal behavior • Suicide attempt

AESI	Atopic Dermatitis
Conjunctivitis	"Narrow" search – Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic Keratoconjunctivitis "Broad" search – Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic Keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia

10.5. 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
      - Preferred Drug Name = Key word "Tacrolimus"
      - Preferred Drug Name = Key word "Pimecrolimus"
   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

2. Require medical review 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	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	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

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
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	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 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	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
Surgical and medical procedures	Therapeutic procedures NEC	Salvage therapy	10068833

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