Title: An Open-Label Study of Dupilumab in Patients With Atopic Dermatitis Who Participated In Previous Dupilumab Clinical Trials

Protocol: R668-AD-1225.07 and
R668-AD-1225.08 (PL, FI, FR)

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

Statistician: [redacted].

Clinical Trial Manager: [redacted]

Clinical Study Director: [redacted]

Version/Date: Version 2.0 Final / 01Feb2019

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

Study Biostatistician

See appended electronic signature page

[redacted] (Author)

Study Medical Director

"See appended electronic signature page

[redacted] (Approver)

Head of BDM or designee

"See appended electronic signature page

[redacted] (Approver)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
ALT (SGOT)	Alanine aminotransferase
AST (SGPT)	Aspartate aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
CRF	Case report form
DLQI	Dermatology Life Quality Index
EASI	Eczema area and severity index
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of study
EOT	End of treatment
ET	Early termination
GB	Great Britain
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonization
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical rating scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PT	Preferred term
q2w	Once every 2 weeks

q4w	Once every 4 weeks
QOL	Quality of life
qw	Once every week
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-1225 study. Since this is an open-label, non placebo-controlled extension study, there is no hypothesis testing to be performed. Descriptive statistics will be used to summarize efficacy data from this study.

This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. These revisions will be based on review of the study and data. Furthermore, the SAP will be updated for any possible subsequent regulatory filings to clarify the data cutoff used for each regulatory filing.

1.1. Background and Rationale

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus and by scaly and dry eczematous lesions. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to major psychological problems, significant sleep loss, and impaired quality of life that leads to high socioeconomic costs. In industrialized countries the prevalence of AD is estimated to be 15 to 30% for children and 2 to 10% for adults and occurs most often in infants and children with approximately 70 to 85% of cases starting before 5 years of age. Sixty percent of patients with childhood AD are free of symptoms by early adolescence but for 40% the disease continues beyond adolescence. The overall costs for AD are estimated to be similar to those for the treatment of asthma, and in the US the estimated direct costs range from $400 million to $4 billion.

The pathophysiology of AD is influenced by a complex interplay between Immunoglobulin E (IgE)-mediated sensitization, the immune system, and environmental factors. The primary skin defect may be an immunologic disturbance that causes IgE-mediated sensitization, with epithelial-barrier dysfunction that is the consequence of both genetic mutations and local inflammation.

Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the patho-physiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via IgE- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute, exudative skin lesions, chemokine 'C' receptor ($CCR4^+$) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5; whereas Type 1 helper T (Th1) cells 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 (TSLP), in AD lesions which may amplify and sustain the allergic response.

The goal in treating AD is to reduce skin inflammation and relieve symptoms. Therapy has been focused on trying to control the T helper cell response. The pharmacological treatment of AD is primarily conducted with topical medications. Topical corticosteroids are the most frequently prescribed class of drugs; however, long term application of topical corticosteroids is not recommended because of the risk of irreversible skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption. Topical calcineurin inhibitors are both effective and safe as short-term treatments, but systemic absorption raises the concern of skin malignancies and increased risk of lymphomas. Repeated application of any topical therapy over a long period of time leads to reduced patient compliance. Antihistamines, which are primarily sedating, are widely prescribed for acute symptomatic treatment of pruritus. Oral immunosuppressants and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Biological agents including anti-tumor necrosis factor (TNF) α, anti–IgE (omalizumab), anti-IL-5 (mepolizumab), and anti-CD11a (efalizumab) have generally been ineffective in clinical trials.

Up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression. Dupilumab (the international non-proprietary name for REGN668, accepted by the World Health Organization and published in February 2013), 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 blockade of the function of both IL-4 and IL-13 signal transduction. Dupilumab is under development as a potential novel treatment for AD, an alternative to oral corticosteroids, calcineurin inhibitors, and other systemic immunosuppressive drugs such as methotrexate, cyclosporine, and azathioprine, which have numerous and considerable side effects. In addition, the broad immunosuppression caused by these drugs carries an increased risk of developing serious bacterial, fungal, viral, and mycobacterial infections, compared with the targeted Th2 inhibition.

The primary purpose of the study is to collect long-term safety data on patients treated with dupilumab to better understand the safety profile and help fulfill the anticipated safety database requirements for long-term exposure. The study investigates dupilumab 300 mg qw, the higher of 2 dose regimens administered in confirmatory Phase 3 clinical trials. Eligible patients are recruited from prior dupilumab controlled trials. Eligible patients must have received any study treatment and completed the specified assessments in the prior dupilumab controlled study or have been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416), but could not be randomized because of randomization closure. This study may provide useful information regarding immunogenicity incidence upon re-exposure to dupilumab and any impact of anti-dupilumab antibodies on functional dupilumab serum (trough) concentration and associated clinical parameters.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of study R668-AD-1225 is to assess the long-term safety of dupilumab administered to adult patients with AD.

1.2.2. Secondary Objectives

The secondary objectives of the study are to assess the immunogenicity of dupilumab in adult patients with AD, in the context of re-treatment, and to monitor efficacy parameters associated with long-term treatment.

1.2.3. Modifications from the Statistical Section in the Final Protocol

The final protocol version is the global protocol amendment 7 dated 02Jun2017 followed by country specific protocol amendments for Great Britain (GB) dated 02Jun2017, Germany, Hungary and Japan dated 05Jun2017; and protocol amendment 8 for Poland dated 04Jan2018, Finland and France dated 08Jan2018. Below is a list of modifications from the statistical section in the protocol.

- Removed the efficacy endpoint "Change and percent change from baseline in disease activity scores (EASI, IGA) and domains within scores at prespecified time points through the end of the study". IGA score will be analyzed as a categorical variable instead of as continuous variable based on change and percent change from baseline value. The two endpoints for EASI are now written as "Percentage change from baseline in EASI score at each visit" and 'Change from baseline in EASI score at each visit".
- Modified the efficacy endpoints to clarify the baseline value used to define the change from baseline and percent change from baseline values.
- Removed the endpoints "Number of days on topical medication (per patient-year)", and "Proportion of patients using topical medications over various periods during the study", since the data collection through the concomitant medication CRFs does not support an accurate evaluation of these endpoints.
- Removed the phrase "or lasting ≥ 4 weeks" condition from the AESI criteria for any type of conjunctivitis or blepharitis or keratitis [i.e. Any type of conjunctivitis or blepharitis or keratitis (severe or serious *or lasting ≥ 4 weeks*)] according to recent revision of list of AESIs across the dupilumab program in AD.

1.2.4. Modifications from the Approved Statistical Analysis Plan

The statistical analysis plan (SAP) version 1.0 was approved on 28Apr2016 according to protocol amendment 4 (global) and protocol amendment 5 (local – GB) for the first step analysis.

This SAP version 2.0 is based on protocol amendment 6 dated 05July2016, protocol amendment 7 dated 02Jun2017-05Jun2017, and protocol amendment 8 dated 04Jan2018-08Jan2018. It is the second version of SAP for study R668-AD-1225.

Table 1: Summary of Modification from the Approved Statistical Analysis Plan

Description of statistical changes	Rational
• Remove the four previous analysis subsets (Naïve, Re-treated, Interrupted Treatment, and Continuously Treated) in section 3.1. All outputs will show "total" column summarizing all patients' data together.	The layouts of all outputs are changed to avoid potential confounding factors introduced by between-study variation
• Remove the time to event endpoints in section 4.5 • Remove the topical medications endpoints in section 4.5 • Remove time to AESI, AE leading to treatment withdrawal analysis in section 5.8.1 • Remove several baseline subgroups for efficacy analysis in section 5.7 o Treatment received in the parent studies o Parent studies o EASI-75 relative to baseline of parent study (≥75% improvement from baseline of parent study) responder or non-responder at the end of treatment visit in the parent studies. o IGA 0-1 responder or non-responder at the end of treatment visit in the parent studies. o Baseline IGA score of current study o Baseline EASI score of current study o Baseline moderate-to-severe EASI of current study o Baseline severe EASI of current study o Baseline NRS score of current study o Region for global submission o Region for Japan submission	To avoid potential confounding introduced by between-study variation

Description of statistical changes	Rational
• Add details of study design for protocol amendment 6, 7 and 8. • Clarify gaps in treatment for patients from Germany, Poland, France and Japan under protocol amendment 7, 8 • Clarify that POEM, DLQI, EQ-5D, PGAD, PGAT, ECG, physical exam, research sample for biomarker analysis were removed starting from protocol amendment 6 in section 4.5 and 4.6 • Update the treatment exposure, compliance and duration of observational period calculation in section 5.5 and 5.6 by accounting for the "off-treatment" or "off-study" gap introduced by protocol amendment 7 and 8 • Clarify the TEAE definition in section 5.8.1. AE onset during the "off-study" treatment gap between protocol amendments 6 and 7 are not considered TEAEs. • Update AESI criteria and programming search algorithm in section 4.6.1 and section 10.6 • Add analysis for Ophthalmological Examination in section 4.6.6 and 5.8.6 • Update the analysis visit window mapping in section 6.4 • Update details of ADA analysis in section 5.10, 5.11 • Add a subgroup (prior treatment of dupilumab in parent study) for efficacy analysis in section 5.7	To be consistent with Protocol amendment 6, 7, 8.
• Add planning of second step analysis in section 7 • Add Process to Derive Data Cut-off for the Second Step Analysis in section 10.8	Added details of second step analysis

2. INVESTIGATIONAL PLAN

2.1. Study Design and Randomization

This is a multicenter, open-label extension study to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD who have previously participated in controlled studies of dupilumab or were screened for a phase 3 study (R668-AD-1334 or R668-AD-1416) but could not be randomized because of randomization closure. There is no randomization required for entry into this OLE study.

The parent studies include the following 14 studies.

- R668-AD-0914
- R668-AD-1021
- R668-AD-1026
- R668-AD-1117
- R668-AD-1121
- R668-AD-1224
- R668-AD-1307
- R668-AD-1314
- R668-AD-1334
- R668-AD-1412
- R668-AD-1415
- R668-AD-1416
- R668-AD-1424
- R668-AD-1433

2.2. Sample Size and Power Considerations

Based on the numbers of patients enrolled or screened in the antecedent dupilumab studies, it is anticipated that approximately 2500 patients will be enrolled in this global study. By then end of May2017, the study enrollment is completed. There are 2678 patients enrolled.

No formal sample size or power calculations were performed for this study.

2.3. Study Plan (Schedule of Study Assessment)

The study consists of a screening period, a treatment period and a follow-up period. The dose level, the duration of treatment period and follow-up period were modified for the study through several protocol amendments. These modifications are outlined in Table 1.

Table 2: Study dose level and study duration under each protocol version

Protocol Version	Country	Dose Level (mg)	Duration of Treatment Period	Duration of Follow-up period
Original and amendment 1	Global	200	100 weeks	16 weeks
Amendment 2 and 3	Global	300	100 weeks	16 weeks
Amendment 4	Global	300	148 weeks or until commercially available	16 weeks
Amendment 5 and 6	Great Britain	300	100 weeks	16 weeks
Amendment 6	Global, Hungary, Japan	300	148 weeks or until commercially available	16 weeks
Amendment 7	Global, Hungary	300	148 weeks or until commercially available	12 weeks
Amendment 7*	France, Germany, Poland, Japan	300	Extend treatment period through approximately 31 December 2017	12 weeks
Amendment 7	Great Britain	300	100 weeks	12 weeks
Amendment 8**	Poland, Finland	300	Extend treatment period to up to 5 years (week 260)	12 weeks
Amendment 8**	France	300	Extend treatment period to approximately September 2018	12 weeks

* Note: Under protocol amendment 7 for France, Germany, Poland and Japan, patients who had already completed the End of Treatment visit under protocol amendment 6 were permitted to resume treatment with study drug. Patients who had completed the End of Study visit were permitted to re-enter the study. The treatment period ended for all patients in these countries on or about 31 December 2017.

** Note: Patients in Poland, Finland and France who had completed their End of Treatment/End of Study visit as per amendment 7 were permitted to resume treatment/re-enter the study provided that no more than 12 weeks had elapsed since their End of Study visit. The duration of the overall treatment period for patients in Poland and Finland was extended to 5 years, and to September 2018 for patients in France.

The study flow diagrams under protocol amendment 7 and 8 are provided in Figure 2, Figure 3, Figure 34 and Figure 35 below:

Under protocol amendment 6, the planned study duration was up to three years or until dupilumab became commercially available in the geographic region of the patient. Protocol amendment 7 was adopted in order to permit those patients in France, Germany, Poland and Japan who had already completed three years of treatment to either continue or re-start treatment through 31 December 2017. Patients who were in the 16-week safety follow-up period were permitted to resume treatment. Patients who had an End of Study visit were permitted to re-enter the study after being re-consented. Patients who had completed 3 years of treatment resumed treatment in a newly created series of visits called the "treatment extension" period. All patients were scheduled to have an End of Treatment visit on or around 31 December 2017.

Protocol amendment 8 extended the treatment period for up to 5 years for patients in Poland and Finland and to September 2018 in France. Again, patients who had previously had an End of Treatment visit under Amendment 7 and were in the 12-week safety follow-up period were permitted to resume treatment. Patients who had an End of Study visit were permitted to re-enter the study after being re-consented. This is illustrated in Figure 1.

As a consequence of these two amendments, certain patients from these countries experienced gaps in treatment. One gap occurred between the Amendment 6 end of treatment (EoT) date and resumption of treatment under Amendment 7 for approximately 113 patients with a median duration of gap around 17 weeks and maximum duration of around 33 weeks. In addition, there are approximately 272 patients from Poland, Finland and France who experienced a second treatment gap from the EoT date under Amendment 7 and resumption of treatment under Amendment 8 with a median duration of gap around 10 weeks and maximum duration of around 21 weeks.

Figure 1: Overall Study Flow Diagram Showing the Treatment Gap due to Protocol Amendment 7 and 8

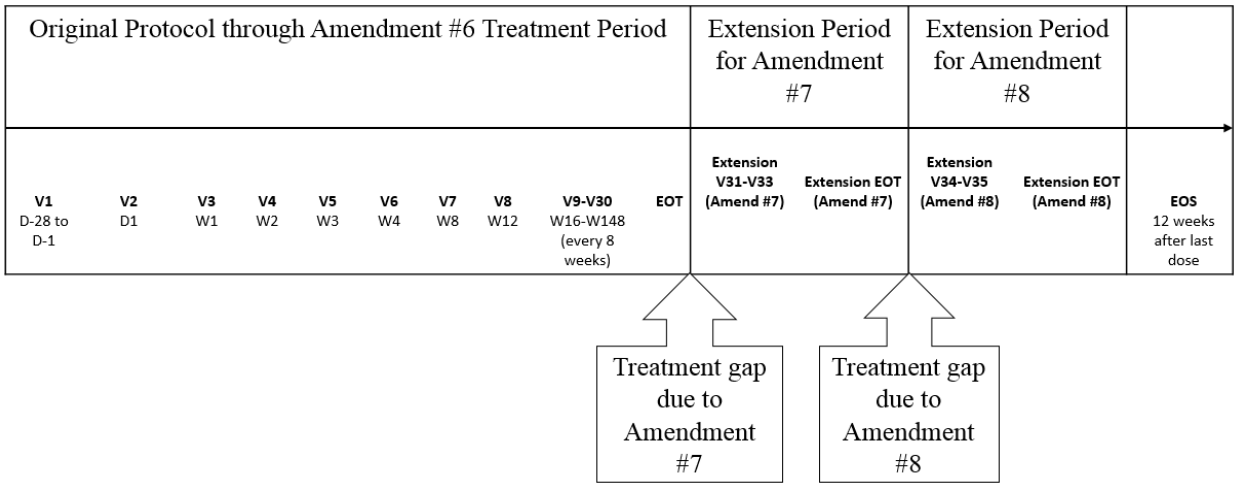
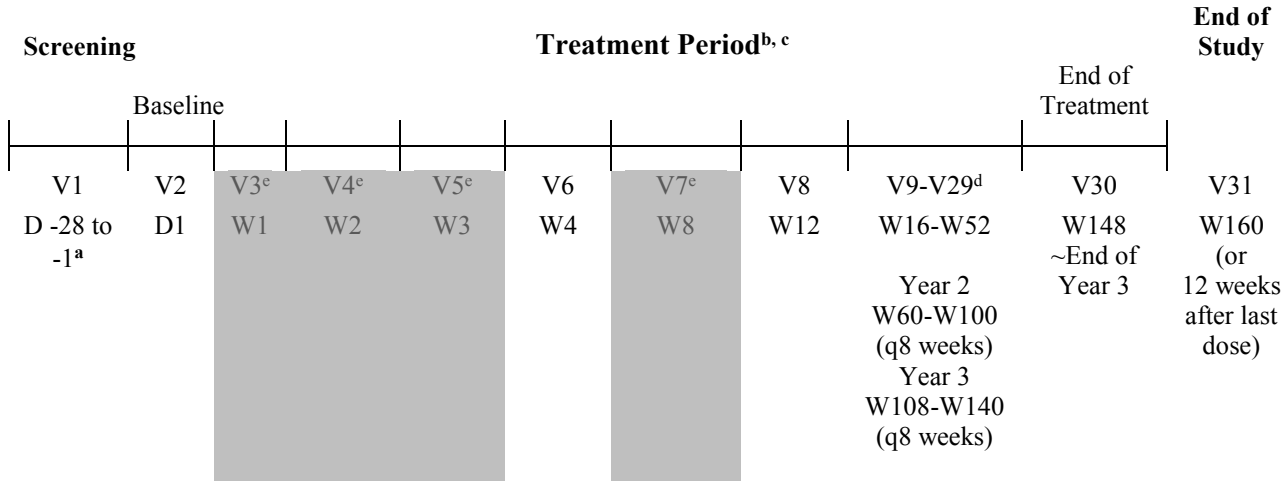


Figure 2: Study Flow Diagram for Protocol Amendment 7 (Global)



[a] Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.

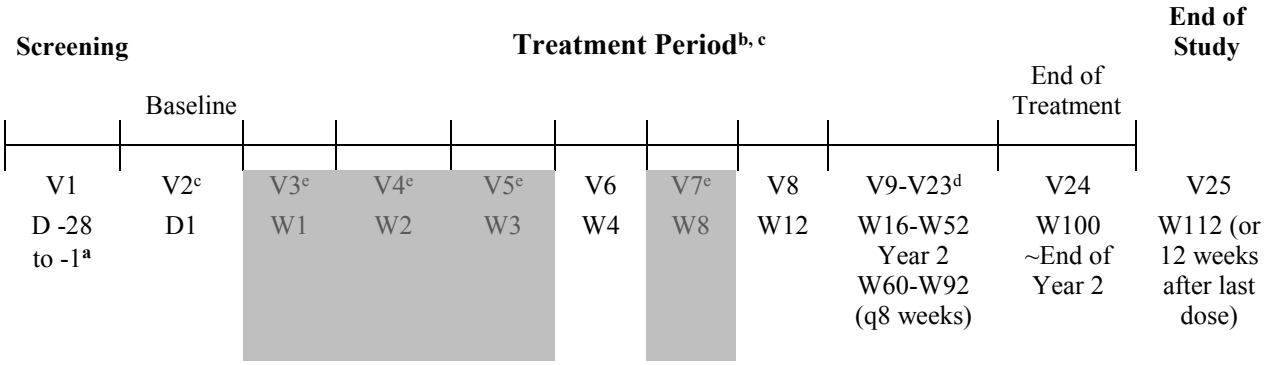
[b] A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8.

[c] Patients will be monitored at the study site for a minimum of 30 minutes at the baseline visit.

[d] Visits 10, 12, 14, and 16 have been removed per amendment 6. This yields a schedule in which visits are 8 weeks apart from week 16 through week 48. The week 48 visit is followed by a visit at 52 weeks, then visits occur every 8 weeks thereafter up to and including the End of Treatment visit (week 148).

[e] Visits 3, 4, 5, and 7 were removed per amendment 6.

Figure 3: Study Flow Diagram for Protocol Amendment 7 (UK)



[a] Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.

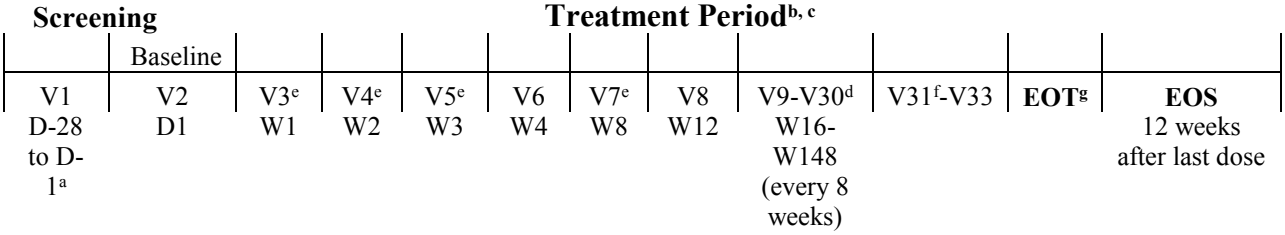
[b] A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8.

[c] Patients will be monitored at the study site for a minimum of 30 minutes at the baseline visit.

[d] Visits 10, 12, 14, and 16 have been removed per amendment 6. This yields a schedule in which visits are 8 weeks apart from week 16 through week 48. The week 48 visit is followed by a visit at 52 weeks. Visits from 60 weeks through the EOT visit occur every 8 weeks.

[e] Visits 3, 4, 5, and 7 were removed per amendment 6.

Figure 4: Study Flow Diagram for Protocol Amendment 7 (France, Germany, Poland, Japan)



[a] Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.

[b] A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8.

[c] Patients will be monitored at the study site for a minimum of 30 minutes at the baseline visit.

[d] Visits 10, 12, 14, and 16 have been removed per amendment 6. This yields a schedule in which visits are 8 weeks apart from week 16 through week 48. The week 48 visit is followed by a visit at 52 weeks, then visits occur every 8 weeks thereafter up to and including the End of Treatment visit (week 148).

[e] Visits 3, 4, 5, and 7 were removed per amendment 6.

[f] Patients who have completed their End of Study (EOS) visit and are resuming treatment per Amendment 7 may re-enter the trial at visit 31 after the trial re-entry visit. Patients who have completed their End of Treatment (EOT) visit may resume treatment at visit 31.

[g] All patients will be scheduled for an EOT visit on or about 31 December 2017.

Figure 5: Study Flow Diagram for Protocol Amendment 8 (Poland, Finland)

Screening		**Treatment Period**[b, c]									
	Baseline										
V1 D-28 to D-1[a]	V2 D1	V3[e] W1	V4[e] W2	V5[e] W3	V6 W4	V7[e] W8	V8 W12	V9-V30[d] W16-W148 (every 8 weeks)	V31[f g]-V43 (every 8 weeks)	**V44/EOT[g]**	**EOS** 12 weeks after last dose

[a] Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.

[b] A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8.

[c] Patients will be monitored at the study site for a minimum of 30 minutes at the baseline visit.

[d] Visits 10, 12, 14, and 16 have been removed per amendment 6. This yields a schedule in which visits are 8 weeks apart from week 16 through week 48. The week 48 visit is followed by a visit at 52 weeks; then visits occur every 8 weeks thereafter up to and including the End of Treatment visit).

[e] Visits 3, 4, 5, and 7 were removed per amendment 6.

[f] Patients who have completed their end of treatment (EOT) visit as per amendment 7 may resume treatment with study drug at the next scheduled visit they would have attended if they had not had an EOT visit.

[g] Patients who have completed their End of Study (EOS) visit as per amendment 7 will be re-evaluated for eligibility at a trial Re-Entry visit. Patients eligible to re-enter the trial may resume treatment at the next scheduled visit they would have attended if they had not completed the study. Patients are not eligible to re-enter the trial if more than 12 weeks have elapsed since their End of Study visit.

The Schedule of Events table for global protocol amendment 7 and protocol amendment 8 for Poland/Finland is presented in Appendix 10.2.

After providing informed consent, patients will be assessed for study eligibility at the screening visit. The screening visit in this study may coincide with the last visit in the previous study, in which case assessments that are common to both studies will be performed only once.

In the original protocol and protocol amendment 1, it stated that “Patients enrolled in this study will receive weekly doses of 200 mg subcutaneous (SC) dupilumab. A loading dose of 400 mg dupilumab (200 mg initial dose, followed by a 200 mg loading dose) will be administered on day 1 (unless last dose administered in the previous AD study is less than 4 weeks before their first dose in the current study, in which case they will receive 200 mg dupilumab), which will allow systemic concentrations to reach steady state faster, and potentially reduce the time to clinical effect.”

Starting from protocol amendment 2, eligible patients received a 600 mg SC dupilumab loading dose (300 mg initial dose, followed by a 300 mg loading dose) on day 1 (unless the last dose administered in the previous dupilumab AD study was less than 4 weeks before their first dose in the current study, in which case they received 300 mg dupilumab; the first dose of 300 mg should be at least 1 week after the last dose in the previous dupilumab study), and then 300 mg SC dupilumab qw starting on day 8. Patients returned for visits as specified in the schedule of events according to the most current protocol amendment for their geographic region.

Patients and/or caregivers who were willing and able to administer dupilumab doses outside the clinic were trained on injecting study drug unless they had already been trained during their participation in the previous study. These patients self-injected study drug (or had the drug administered by a caregiver) during weeks in which no clinic visit was scheduled. Safety, laboratory, and clinical assessments were performed at specified clinic visits.

Patients who received treatment with a prohibited or restricted medication were to be discontinued from study drug for the duration of the prohibited treatment (plus 5 half-lives, as applicable). Study treatment could be resumed in consultation with the medical monitor.

Patients who tested positive for ADA at their last study visit (early termination or end of study) may be asked to return to the clinic to have additional ADA samples collected for analysis.

Samples for clinical chemistry and hematology, drug concentrations and anti-drug antibodies (ADAs) were collected at various time points throughout the study according to the protocol. One sample for DNA analysis was collected from patients who consented to participate in the optional genomic sub-study.

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 will be used for all statistical analyses:

3.1. The Safety Analysis Set (SAF)

The safety analysis set (SAF) consists of all patients who received any study drug. Efficacy, treatment compliance/administration, and all clinical safety variables will be analyzed using the SAF.

3.2. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set consists of all treated patients who had at least one non-missing drug concentrations result following the first dose of study drug.

3.3. The Anti-Drug Antibody (ADA) Analysis Set (AAS) and Neutralizing Antibody (NAb) Analysis Set (NAS)

The ADA population consists of all treated patients who received any study drug and who had at least one non-missing ADA result after the first dose of the study drug.

The neutralizing antibody (NAb) Analysis Set (NAS) consists of all patients who received any study drug and who had at least one non-missing Nab result or who had all samples negative in the ADA assay after first dose of the study drug.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics in Current Study

The following demographic and baseline characteristics variables in current study will be summarized:

- Demographic variables:
  - Age (year)
  - Age group (≥18-<40 year, ≥40-<65 year, ≥65 year) and elder group (≥65 - <75 year, ≥75 - <85 year; ≥85 year)
  - Sex (Male, Female)
  - Ethnicity (Hispanic or Latino, Not-Hispanic or Latino)
  - Race (White, Black or African American, Asian, Other)
  - Baseline Weight (kg)
  - Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)
  - Baseline Height (cm)
  - BMI (kg/m^2)
  - BMI group (kg/m2) (<15, ≥15-<25, ≥25-<30, ≥30)
- Baseline characteristics in current study:
  - Previous AD study number
  - Duration of AD at Day 1 of current study (< 26 years, >=26 years)
  - Previous treatment received in the parent study (placebo, dupilumab)
  - Previous dupilumab dose received in the parent study
  - Pruritus numerical rating scale (NRS)
  - Investigator's Global Assessment (IGA) score
  - Eczema Area and Severity Index (EASI) score
  - Patient global assessment of disease status
  - Patient Oriented Eczema Measure (POEM)
  - Dermatology Life Quality Index (DLQI)
  - EQ-5D
  - Country
  - Geographic region

4.2. Characteristics of Patient Status in Parent Studies

The following variables summarizing baseline disease characteristics in the parent study are defined:

1. Baseline disease characteristics in parent study
   - Investigator's Global Assessment (IGA) score
   - Eczema Area and Severity Index (EASI) score
   - Pruritus NRS
   - Patient global assessment of disease status
   - Patient Oriented Eczema Measure (POEM)
   - Dermatology Life Quality Index (DLQI)
   - EQ-5D

   The baseline value of a patient in the parent study, which is defined as the last non-missing value on or before the first dose date in the parent study, will be derived and summarized for all efficacy assessments. If a patient participated in more than one study before enrolling into AD-1225 study, the baseline value of the earliest parent study will be used and summarized. For example, for a patient who entered from AD-1415 (SOLO-CONTINUE) study, the baseline value of the patient in the parent study is the baseline value in the SOLO studies (either AD-1334 or AD-1416) in which the patient participated before rollover into the AD-1415 study.
2. The following variables for patient status at the end of treatment visit in the parent study (defined as the scheduled end of treatment visit in the parent study protocol [e.g., Week 16 for a parent study with a 16-week treatment period]) will be derived and summarized:

   Number and percentage of patients:
   - Achieving IGA 0 or 1
   - Achieving EASI-75 (>=75% reduction in EASI scores from baseline of the parent study)
   - Achieving EASI-50 (>=50% reduction in EASI scores from baseline of the parent study)
   - Achieving EASI-90 (>=90% reduction in EASI scores from baseline of the parent study)
   - Achieving improvement (reduction) of pruritus NRS >=4 from baseline of the parent study
   - Achieving improvement (reduction) of pruritus NRS >=3 from baseline of the parent study

Patients with a missing value at end of treatment visit in the parent study after censoring for rescue treatment use or study withdrawal will be counted as non-responders at the end of treatment visit in the parent study. For patients who had been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416) but could not be randomized because of randomization closure, the patient's status at end of treatment visit in the parent study will be blank. For patients from the 4-week treatment period of phase I or II studies (i.e. R668-AD-0914, R668-AD-1026 and R668-AD-1121), the patient's status at end of treatment visit in the parent study will be blank, since most patients have shown non-response to treatment after a treatment duration of only 4 weeks.

3. The treatment gap between the date of the last dose of dupilumab in the parent study and the first dose date in the current study will be derived and summarized by the following categories: ≤8 weeks, >13 weeks.

4. The following variables for patients' exposure to dupilumab in the parent study will be provided:

   - Cumulative dupilumab dose (mg) in the parent study. For patients who participated in more than one parent study (e.g. patients enrolled in R668-AD-1415 study who previously participated in R668-AD-1334 or R66-AD-1416 study) the cumulative dupilumab dose in parent study is the sum of all dupilumab doses received in all parent studies.
   - Duration of treatment of dupilumab (in weeks) in the parent study, defined as date of last dupilumab injection – date of first study drug injection) + 7]/7. The duration will be categorized by ≤ 4 weeks (ie. 28 days), 5-≤12 weeks, 13-≤16 weeks 17-≤24 weeks, 25-≤52 weeks and >52 weeks.

4.3. Medical History and Atopic Disease Medical History

Medical history will be coded to a Preferred Term (PT), high level term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO.

The atopic disease (AD) medical history 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. The AD medical history was collected through atopic / allergic disease history case report form (CRF) in the parent study and will be summarized in current study.

4.4. Pre-treatment / Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

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

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

Treatment with the following concomitant medications is prohibited during the study:

- Treatment with nonsteroidal systemic immunosuppressive medications (including, but not limited to, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, or other immunomodulating biologics).
  - Systemic corticosteroids were removed as a prohibited medication as of Amendment 7.
- Treatment with an investigational drug (other than dupilumab)
- Live (attenuated) vaccines

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

If medically necessary, patients may receive prohibited medication(s) at the discretion of the investigator (e.g., as rescue treatment for intolerable AD symptoms or to manage serious intercurrent conditions). However, patients who receive prohibited medication(s) will be discontinued from study drug for the duration of treatment with these prohibited medications, plus 5 half-lives. These patients will be asked to continue with the assessments of the early termination and end of study visits.

4.5. Efficacy Variables

Analysis of efficacy variables will be performed in the overall SAF population, as described in Section 3.1.

Starting from protocol amendment 6, the following assessments were removed from the schedule of events. All available data collected prior to implementation of protocol amendment 6 will still be summarized.

- POEM
- Dermatology Life Quality Index (DLQI)
- EQ-5D
- Patient Global Assessment of Disease Status
- Patient Global Assessment of Treatment Effect

All efficacy related endpoints for this study are secondary endpoints. Secondary endpoints include:

- Key secondary endpoints
  - Proportion of patients with IGA score of either 0 or 1 at each visit
  - Proportion of patients with EASI-75 relative to baseline of parent study (≥75% reduction in EASI scores from baseline of parent study) at each visit
- Other secondary endpoints
  - Proportion of patients with low disease activity state (ie., IGA ≤2) at each visit
  - Proportion of patients achieving an IGA reduction of >=2 from Day 1 of current study at each visit for patients with Day 1 IGA score of current study >= 2
  - Percentage change from Day 1 of current study in EASI score at each visit
  - Percentage change from baseline of parent study in EASI score at each visit
  - Change from Day 1 of current study in EASI score at each visit
  - Change from baseline of parent study in EASI score at each visit
  - Proportion of patients with EASI-50 relative to baseline of parent study (≥50% reduction in EASI scores from baseline of parent study) at each visit
  - Proportion of patients with EASI-90 relative to baseline of parent study (≥90% reduction in EASI scores from baseline of parent study) at each visit
  - Percent change from Day 1 of current study in pruritus NRS at each week
  - Percent change from baseline of parent study in pruritus NRS at each week
  - Change from Day 1 of current study in pruritus NRS at each week
  - Change from baseline of parent study in pruritus NRS at each week
  - Proportion of patients with improvement (reduction) of pruritus NRS ≥4 from Day 1 of current study or achieving NRS score of 0 at each visit
  - Proportion of patients with improvement (reduction) of pruritus NRS ≥4 from baseline of parent study or achieving NRS score of 0 at each visit
  - Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from Day 1 of current study or achieving NRS score of 0 at each visit

- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline of parent study or achieving NRS score of 0 at each visit
- Proportion of patients requiring rescue treatment:
  - Overall
  - Systemic treatment
    - Systemic corticosteroids
    - Systemic immunosuppressive drugs
  - Phototherapy
- Changes from Day 1 of current study in DLQI
- Changes from baseline of parent study in DLQI
- Changes from Day 1 of current study in POEM
- Changes from baseline of parent study in POEM
- Percent changes from Day 1 of current study in POEM
- Percent changes from baseline of parent study in POEM
- Changes from Day 1 of current study in EQ-5D
- Changes from baseline of parent study in EQ-5D
- Patient global assessment of disease severity at each visit through the end of the study
- Patient global assessment of treatment effect at each visit through the end of the study

Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin 2001). The EASI score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section.

The EASI will be collected at the scheduled and unscheduled clinic visits as indicated in Section 10.2.

Investigator's Global Assessment (IGA)

The IGA is a static 5-point measure of AD disease severity used in clinical studies to determine severity of AD and clinical response to treatment. 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 the scheduled and unscheduled clinic visits as indicated in Section 10.2.

Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a simple assessment tool that patients will use to report the average intensity of their pruritus (itch), during a 1 week recall period. Patients will access the IVRS/IWRS weekly, preferably around the same time each week, and be asked the following question:

- For average itch intensity: "On a scale of 0 – 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch overall, which is on average, during the past week?"

Patients will be trained on using the IVRS/IWRS to record their Pruritus NRS score at the baseline visit, and visit 6, and will be queried by site staff for compliance at each scheduled (and any unscheduled) clinic visit.

The baseline NRS is defined as the last NRSs reported prior to the first dose of study drug.

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 (ie, 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; 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.

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 skin diseases such as AD on dermatology-related Quality of Life (QoL). Domains measured include daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work and school. The format is a simple response to 10 items, which assess QoL over the last week. Each DLQI item has four response categories ranging from "Not at all" (0) to "Very much" (3). "Not relevant" is also a valid response, and it is also scored as 0. Question 7 includes a response of "Yes", which is scored as 3. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked. 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. The DLQI total score is a sum of the 10 questions. Total score ranges from 0 to 30, and higher scores indicate greater HRQOL impairment. If only one of the 10 questions is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

EQ-5D

The EuroQOL 5-Dimension Health Questionnaire (EQ-5D) is a standardized measure of health status developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economic appraisal (Greiner 2005). The EQ-5D as a measure of health related QOL, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health."

The 5 dimensional 3-level systems are converted into a single index utility score. Values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model and weighted according to the social preferences of the UK population. The minimum value for the single index utility score is –0.594, The Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcomes as judged by the individual respondents. EQ-5D self-reported VAS data generates information on the self-perceived overall health-related quality of life. Appendix 10.4 provides the SAS code to derive the index utility score using UK based population.

Patient Global Assessment of Disease Status

Patients will rate their overall wellbeing based on a 5-point Likert scale. Patients will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing". Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5).

Patient Global Assessment of Treatment Effect

Patients will rate their satisfaction with the study treatment based on a 5-point Likert scale. Patients will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor" (1); "Fair" (2); "Good" (3); "Very Good" (4); "Excellent" (5).

The questionnaires (POEM, DLQI, and EQ-5D) will be administered only to the subsets of patients who speak fluently the languages in which the questionnaire is presented (based on availability of validated translations in participating countries).

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events Variables

The primary endpoint in the study is the incidence and rate (events per patient-year) of treatment-emergent adverse events (TEAEs) through the last study visit.

The key secondary endpoints related to AE is

- Incidence and rate (events per patient-year) of SAEs and AEs of special interest

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, latest version).

An **Adverse Event** is any untoward medical occurrence in a patient 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.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy

The pre-treatment period is defined as the period from the subject providing informed consent up to the first dose of study drug in current study.

The treatment period is the period starting from the first dose date up to the last dose date + 7 days. As there are two gaps in treatment due to protocol amendment 7 and 8, the gaps in treatment are not included as part of the treatment period.

The follow-up period is the period starting 1 day after end of treatment period up to the end of study visit. As some patients were allowed to complete the follow-up period under protocol amendment 6 then re-enter the study, or were allowed to complete the follow-up period under protocol amendment 7 and then re-enter the study, the follow-up period consists of all the separate follow-up periods under protocol amendment 6, 7 and 8.

The overall study period consists of treatment and follow-up period.

The pre-treatment AE and treatment emergent AE (TEAE) are defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during pre-treatment period.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the Day 1 of current study during the treatment and follow-up period. As the protocol indicated that 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 with onset during the treatment and follow-up period are considered as TEAEs. So TEAE includes all AE onset during the treatment period and during follow-up period.

Under protocol amendment 7, patients in France, Germany, Poland and Japan who had completed their end of study visit under protocol amendment 6 were permitted to re-enter the study. Similarly, under protocol amendment 8, patients in Poland, Finland and France who had already completed their end of study visit under protocol amendment 7 were permitted to re-enter the study.

Treatment discontinuation required under protocol amendment 6 followed by resumption of treatment permitted under protocol amendment 7 resulted in a gap in treatment for certain patients in these four countries. There was a similar treatment gap for certain patients in Poland, Finland and France who had an EoT/EoS visit under amendment 7 and subsequently resumed treatment under amendment 8.

Hence any AE with an onset between the end of study visit under protocol amendment 6 and the date of first injection under amendment 7; or between end of study visit under protocol amendment 7 and date of first injection under amendment 8 is **not** considered TEAEs.

The list of adverse events of special interest (AESI) was revised several times. Below is the AESI list under protocol amendments 4 and 5:

- Anaphylactic reactions
- Acute allergic reaction
- Severe injection site reactions that last longer than 24 hours
- Mycosis fungoides
- Cutaneous T-cell dyscrasia
- Any severe infection
- Any infection requiring treatment with parenteral antibiotics
- Any infection requiring treatment with oral antibiotics/anti-viral/anti-fungal for longer than 2 weeks
- Any clinical endoparasitosis
- Any opportunistic infection

Under protocol amendment 6, suicide-related events and certain eye-related events were added as AESIs. Under protocol amendment 7, the list of AESI are as follows:

- Anaphylactic reactions
- Systemic or extensive hypersensitivity reactions
- Malignancy (except basal cell carcinoma)
- Helminthic infections
- Any suicide-related events
- Any type of conjunctivitis or blepharitis, or keratitis (severe or serious)

The SAP summarizes AESIs according to the most current list under protocol amendments 7 and 8. The definition of AESI is same under protocol amendment 7 and 8.

Appendix 10.6 provides a list of AESIs search criteria.

4.6.2. Laboratory Safety Variables

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

Blood Chemistry

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

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be 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 by the central lab 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

Pregnancy serum or urine testing will be performed for all women of childbearing potential.

4.6.3. Vital Sign Variables

The following vital signs parameters will be collected:

- Respiratory rate (bpm)
- Heart rate (bpm)
- Systolic and diastolic blood pressures (mmHg)
- Body temperature (^{o}C) with the measure method (oral/tympanic/axillary/rectal)

Heart rate and blood pressure will be obtained with the patient in sitting position after the patient has rested comfortably for at least 5 minutes. Vital signs will also be taken at 30 (+/- 10) minutes post-injection at visits 2, 3, and 4, during the in-clinic 30-minute post-injection observation.

4.6.4. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval ($QTcF=QT/[RR^{0.33}]$ and $QTcB=QT/[RR^{0.5}]$) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws.

ECG measurement was removed from the schedule of events starting from protocol amendment 6.

4.6.5. Physical Examination Variables

A thorough and complete physical examination will be performed. The physical examination variable values are dichotomized to normal and abnormal.

Physical examination was removed from the schedule of events except for the baseline assessment starting from protocol amendment 6.

4.6.6. Ophthalmological Examination

Starting from protocol amendment 6, the ophthalmological examination was added to the schedule of events. This exam will be performed for certain patients of interest, as determined by the sponsor medical monitor in consultation with the investigator, at select study centers that have access and can refer patients to an eye specialist, either a General ophthalmologist or a Cornea and External Eye Disease (‘front-of-the-eye’) subspecialty expert. Any baseline findings will be documented as part of the patient’s medical history and/or physical exam, as appropriate. Any inflammatory ophthalmological condition that occurs post-baseline will be captured as an AE. Additional tests and assessments may be performed to help understand the AEs. The method and procedure for the exam are provided in the study reference manual.

The ophthalmological exam data includes:

- Past ocular history
- Past and current treatment of ophthalmology
- Ophthalmic adverse event assessment
- Ophthalmological examination and procedures
- Intraocular pressure
- Slit lamp biomicroscopy
- Indirect ophthalmoscopy

4.7. Pharmacokinetic (PK) Variables

Samples for drug concentration will be collected at time points according to Appendix 10.2. PK variables consist of functional dupilumab concentration and time (both actual and nominal).

4.8. Antibody (ADA) Variable

ADA variables include the ADA status, titer, neutralizing antibody (NAb) status, and time-point/visit. ADA samples will be collected at the clinic visits according to Appendix 10.2.

4.9. Biomarkers Variables

Research samples, optional genomics substudy, and exploratory biomarker testing assessments was removed from the schedule of events starting from protocol amendment 6. Prior to protocol amendment 6, the following biomarkers were collected in this study:

- TARC
- total serum IgE
- hs-CRP, ANA, anti dsDNA, anti-TPO

Thymus and activation-regulated chemokine and total serum IgE are markers of Th2 activity and are downstream of IL-4/IL-13 signaling. These analytes will be assessed as measures of Th2 activity and drug effect (PD). These results may also be used for modeling dupilumab activity with drug levels in the comparison of dosing regimens. Thymus and activation-regulated chemokine levels have also been closely associated with AD disease activity and severity, and will be evaluated as an exploratory marker of efficacy. These markers may also be assessed for their potential value in predicting treatment response.

Th2 and Th1 immune functions are believed to play a role in regulating each other. To determine whether or not there is a change in non-Th2 mediated inflammation, hs-CRP, as well as autoantibodies anti-dsDNA, anti-TPO, and ANA will be measured.

5. STATISTICAL METHODS

All data including both safety and efficacy will be summarized overall for all patients in SAF.

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, Q1 (25% percentile), Q3 (75% percentile), standard deviation, minimum, and maximum.

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

5.1. Demographics and Baseline Characteristics

5.1.1. Demographics and Baseline Characteristics of Current Study

The following demographics and baseline characteristics of current study as specified in Section 4.1 will be summarized overall for all patients in SAF.

- Demographics,
- Baseline characteristics in current study

5.1.2. Characteristics in Parent Study

The following demographics and baseline characteristics from the parent study as specified in Section 4.2 will be summarized overall for all patients in SAF.

- Baseline characteristics in parent study,
- End of treatment status of a patient in the parent study,
- Duration of off treatment period (days) before baseline
- Duration of patient exposure to dupilumab in the parent study

5.2. General Medical History and AD History

Medical history in current study will be summarized by primary SOC and PT. The table will be sorted by decreasing frequency of SOC followed by PT. Medical history will be listed.

AD medical history will be summarized by number and percentage of patients with each type of AD medical history.

5.3. Pre-treatment/Concomitant Medications/Procedures

Number and proportion of patients taking prior/concomitant medication will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4. Patients will be counted only once for each medical class (ATC level 2 and 4) linked to the medication.

Listing of pre-treatment medication and concomitant medications will include generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, route.

5.4. Subject Disposition

The following summaries by table will be provided for all patients in SAF:

- The total number of screened patients
- The total number of enrolled patients
- The total number of patients enrolled and reconsented under each protocol amendment
- The total number of patients in each analysis set
- The total number of patients who completed the study including a summary of patients who completed the study under each protocol amendment, completed up to week 52, completed up to week 100, complete up to week 148, completed up to week 156, completed up to week 208, completed up to week 260, and completed up to week 272
- The total number of patients who discontinued the study and the reasons for discontinuation
- The total number of patients who completed study treatment including a summary of patients who completed treatment under each protocol amendment
- The total number of patients who discontinued the study treatment and the reasons for discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation cumulatively by visits (i.e. end of week 1, end of week 2, end of week 4, end of week 8, end of week 12, end of week 16, end of week 24, end of week 36, end of week 48, end of weeks 52, end of week 76, end of week 100, end of week 124, end of week 148, end of week 164, end of week 208, end of week 260, end of study). The visits in weeks are categorized based on study days from the first dose date in current study. For example, end of week 1 corresponds to study day 8.

As patients from different countries can have different study duration and treatment duration according to the country specified protocol amendment, subgroup analysis of the disposition data by country of interest will be provided.

The following listings will be provided:

- Listing of subject disposition including: date of enrollment, date of the last visit, received dose, completed study or discontinued by reason, a flag indicating if a patient completed study under protocol amendment 6 then retry into study under protocol amendment 7
- A listing of patients enrolled but not treated
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation, summary tables of reasons will be provided
- A listing and a summary table of major protocol deviations will be provided

5.5. Dupilumab Dose administration

The compliance with protocol-defined investigational product will be calculated as follows:

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

Loading doses for the same patient will be counted as 1.

Treatment compliance will be calculated and summarized for the following periods of interest.

- Overall study treatment period
- The treatment period prior to “treatment gap” (defined below)

  As shown in Figure 1 of Section 2.3, due to the implementation of protocol amendments 7 and 8, patients in certain countries experienced a gap in treatment between completion of the treatment period under a prior protocol amendment and the beginning of a new protocol amendment. Specifically, there are two types of treatment gaps:

  - Patients from Germany, France, Poland and Japan who completed the 3-year treatment period under protocol amendment 6, and resumed dupilumab treatment after reconsenting to amendment 7.
  - Patients from Poland, Finland and France who completed the treatment period under protocol amendment 7 and resumed treatment after reconsenting to protocol amendment 8.

- The "continuous-treatment" period (defined below)

  For the QW regimen being evaluated in this study, the decline in concentrations of dupilumab following an interruption in treatment of ≤ 8 weeks is not expected to be sufficient to have a substantial impact on the pharmacodynamic effect of dupilumab. For patients with a treatment gap ≤ 8 weeks, a "continuous-treatment" period is defined as the combined prior to "treatment gap" period and "post-gap" period. For patients who did not reconsent to protocol amendment 7 or 8, the "continuous-treatment" period is the study treatment period.

- The treatment extension period under protocol amendment 7 for patients from Germany, Poland, France and Japan who completed 3-year treatment
- The treatment extension period under protocol amendment 8 for patients from Poland, Finland and France who reconsent to protocol amendment 8

Treatment compliance during both "treatment extension" periods will be summarized. Number of patient with each type of gap in treatment and duration of gap will be summarized.

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: <80%, and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections and dosing information will be presented.

5.6. Treatment Exposure and Observation Period

The duration of treatment exposure period during the study in week is calculated as:

[(Date of last study drug injection – date of first study drug injection) + 7]/7

regardless of unplanned intermittent discontinuations. For the exposure calculation, the two treatment gaps due to patients resuming treatment under protocol amendment 7 or 8 will be excluded. The duration of exposure will be summarized using number of patients, means, SD, minimums, medians, and maximums. A summary of the number of doses will also be provided.

The duration of observation period during the study in weeks is calculated as:

[(Date of the last visit – date of the first study medication dose) +1]/7.

For the duration of observation period calculation, the study gap for patients who have completed the study under protocol amendment 6 then retry into the study under protocol amendment 7 will be excluded.

The duration of observation periods will be summarized using number of patients, means, SD, minimums, medians, and maximums. The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as: ≥ 1 week, ≥ 4 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 24 weeks, ≥ 52 weeks, ≥ 76 weeks, ≥ 100 weeks, ≥ 104 weeks, ≥ 124 weeks, ≥ 148 weeks, ≥ 156 weeks, ≥ 164 weeks, ≥ 208 weeks, ≥ 260 weeks, ≥ 272 weeks.

As of protocol amendment 2, the weekly dose of dupilumab was changed from 200 mg to 300 mg. The number of patients exposed to 200 mg dose, the number of 200 mg doses and duration of treatment exposure with 200 mg and 300 mg in weeks will be calculated and summarized separately.

Appendix 10.10 provides the detailed algorithm for calculating duration of treatment exposure and observational period.

5.7. Analyses of Efficacy Variables

The efficacy variables will be summarized for all patients in SAF. The continuous efficacy variables will be summarized using number of patients, means, SD, minimums, medians, Q1, Q3 and maximums. Categorical efficacy variables will be summarized using patient counts and proportion. No formal statistical hypothesis testing will be performed. The graph of mean value for continuous variable or proportion for categorical variable by visit will be provided.

All observed values, regardless of whether rescue treatment is used or data is collected after withdrawal from study treatment will be used for analysis. No missing values will be imputed.

For the categorical efficacy variables, the proportion of patients with each response at each visit will be calculated using the number of patients with a non-missing value at the visit as the denominator.

As described in Section 5.6, there are up to two potential “treatment gaps” due to patient re-entry to the study for protocol amendments 7 and 8 for patients from Germany, France, Poland and Japan. The primary focus of the efficacy data will be on the data collected prior to these potential “treatment gaps”.

- If the “treatment gap” is ≤8 weeks, then all efficacy data will be summarized together, i.e. data will be analyzed as if the patient had been dosed continuously

- If the “treatment gap” is >8 weeks, efficacy data collected before and after the treatment gap will be summarized separately.

Data collected under end of study visit (i.e. off-treatment measurement at the end of 12-week or 16-week safety follow up period) will be summarized separately from the data while the patient was on treatment.

For the analysis of Pruritus NRS, the weekly NRS collected during the safety follow-up period, during the treatment gap between amendments 6 and 7, and between amendments 7 and 8 will be separated from the NRS collected during treatment. The primary focus of NRS data will be on the data collected during treatment.

Subgroup analyses for efficacy

Different subgroups within the overall SAF population will be defined as below. The analyses will be performed for the secondary efficacy variables related to EASI, IGA and pruritus NRS by:

- Duration of AD at Day 1 of current study (< 26 years, ≥26 years)
- Baseline body weight of current study ((<70 kg, ≥70-<100 kg, ≥100 kg)
- Baseline BMI of current study (<15, [15-25), [25-30), ≥30)
- Age (≥18-<40, ≥40-<65, ≥65)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Others)
- Ethnicity: Hispanic or Latino (yes/no)
- Previous usage of ciclosporin (CsA) (Yes, No)
- Previous usage of methotrexate (MTX) (Yes, No)
- Previous usage of Azathioprine (Aza) (Yes, No)
- Previous use of systemic immunosuppressants for AD (Yes, No)
- History of asthma (Yes, No)
- History of nasal polys (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergies (Yes, No)
- Previous treatment of dupilumab in parent study (Yes, No)
  - For patients who received dupilumab in parent study, data from the following two subgroups will also be summarized.
    - Re-treatment (treatment gap > 8 weeks): – Patients who came from the dupilumab arms of parent studies, and if the gap period between the last dupilumab study drug injection in parent study and the first study drug injection in current study is > 8 weeks (greater than 64 days).
    - Continuous treatment (gap ≤ 8 weeks) – patients who came from the dupilumab arms of parent studies, and if the gap period between the last dupilumab study drug injection in parent study and the first study drug injection in current study is ≤ 8 weeks (less than or equal to 64 days).

5.8. Analysis of Safety Data

The summary of safety and tolerance will be performed for all patients in 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 (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 10.3. The baseline when determining treatment-emergent PCSV refers to the baseline value of current study.

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 or African American, Asian, Other)
- Duration of AD based on data from parent studies (< 26 years, ≥26 years)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)

5.8.1. Adverse Events

Listings of TEAEs, serious TEAEs, TEAEs resulting in death and study drug discontinuation will be generated.

Number and proportions of patients reporting TEAEs will be summarized for the following TEAEs, sorted by the decreasing frequency of SOC, HLT and PT:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - Common TEAEs by SOC/HLT/PT (incidence with HLT ≥5%)
  - Common TEAEs by SOC/HLT/PT (incidence with PT ≥5%)
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - TEAEs related to study medication as assessed by the investigator by SOC/PT

  - Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
- Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLT/PT
  - Serious TEAEs related to study medication as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- Death by SOC/PT

In addition, the number of events per 100 patient-year (NEPY) and number of patients with at least one event per 100 patient-years (EAIR) will be calculated and summarized for the following:

- TEAEs by SOC and PT
- Severe TEAEs by SOC/PT
- TEAEs related to study medication as assessed by the investigator by SOC/PT
- Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
- Serious TEAEs by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- AESI by AESI category and HLT/PT

These calculations will be adjusted for the duration of the TEAE period. The detailed methodology of NEPY and EAIR is described in Appendix 10.5.

5.8.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of patients with abnormal lab value during study whose screening and baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs during study, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by subject and visit will be provided.

The graph of mean change and/or percentage change from baseline value for lab parameters by visit will be provided.

5.8.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSV, depending on data
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings will be provided with flags indicating the treatment-emergent PCSVs, depending on data.

5.8.4. Physical Exams

The number (n) and percentage (%) of patients with abnormal physical exams will be summarized at the scheduled visits. A summary of treatment-emergent abnormal findings will be provided.

5.8.5. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of patients 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.

5.8.6. Analysis of Ophthalmological Examination

For those patients enrolled in the optional ophthalmology sub study, the ophthalmology exam data will be included as a subset of the safety analysis set. Patients in the safety analysis set who enrolled in the ophthalmology sub-study will be categorized into subgroups based on whether or not they had an existing ophthalmological AE at the time of sub-study entry.

- No ophthalmological AE
- At least one ophthalmological AE
    - Ended prior to sub-study entry
    - Ongoing at sub-study entry

Summary of ophthalmological exam data will be performed for all patients in the safety analysis set who enrolled in the ophthalmology sub-study and by the above defined subgroups (i.e. ophthalmological AE or not at the sub-study entry) using descriptive statistics and will include:

- Summary of patient disposition
- Summary of demographic and baseline characteristics of current study
- Summary of past ocular history
- Summary of past and current treatment of ophthalmology
- Summary of concomitant medications and procedures taken during the ophthalmology sub-study
- Summary of Treatment Emergent Ophthalmology Adverse Events (TEAE) Onset during the Ophthalmology Sub-study (i.e. between the inform consent date of sub-study up to the last visit of sub-study) by SOC/PT
- Summary of Ophthalmic Adverse Event Assessment
- Summary of Ophthalmological Examination and Procedures
- Summary of observed intraocular pressure and its change from baseline at the beginning of sub-study
- Slit lamp biomicroscopy, shift table for normal/abnormal status for each test
- Indirect ophthalmoscopy shift table for normal/abnormal status for each test

5.9. Analysis of Pharmacokinetic Data

For this study, sampling will be sparse and the types of analyses will be:

- Descriptive statistics at each sampling time

No formal statistical analysis will be performed within the scope of this plan. For the descriptive statistical analysis, concentrations below the lower limit of quantitation (LLOQ) will be set to zero.

5.10. Analysis of ADA Data

5.10.1. Analysis of ADA Data

The ADA variables described in Section 4.8 will be summarized using descriptive statistics in the ADA analysis set. Frequency tables of the proportion of patients with pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent ADA responses, and titer categories will be presented as absolute occurrence (n) and percent of patients (%).

- Pre-existing immunoreactivity is defined as either an ADA positive response in the assay at baseline of parent study with all ADA results negative post first dose of the current study, OR a positive response at baseline of parent study with all ADA results less than 4-fold baseline titer levels of parent study, post first dose of the current study.
- Treatment emergent response is defined as a positive response in the ADA assay post first dose of current study when baseline results of parent study are negative or missing. The treatment emergent responses will be further characterized as Persistent, Indeterminate or Transient
  - Persistent Response – defined as a treatment emergent ADA response with two or more consecutive ADA positive sampling time points separated by greater than (>) 12-week period (greater than 84 days), with no ADA negative samples in between.
  - Indeterminate Response – defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
  - Transient Response - defined as a treatment emergent ADA positive assay response that is not considered persistent or indeterminate.
- 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 of parent study, when baselines results of parent study are positive.

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

- Titer Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

5.10.2. Analysis of Neutralizing Antibodies (NAb)

The absolute occurrence (n) and percent (%) of treatment-emergent or treatment boosted ADA positive patients that are positive in the NAb assay will be summarized for patients in the NAb analysis set.

5.11. Association of Immunogenicity with Exposure, Safety and Efficacy

5.11.1. Immunogenicity and Exposure

Associations between ADA and systemic exposure to dupilumab may be explored. Plots of dupilumab concentration may be provided for analyzing the potential impact of treatment-emergent, persistent and titer ADA responses (high, moderate or low) on PK.

5.11.2. Immunogenicity and Treatment Gaps

Associations between ADA (e.g. ADA status, ADA maximum titers, and neutralizing antibody status) and treatment gaps (i.e. ≤8 weeks or >8 weeks) due to patients resuming treatment under protocol amendment 7 or 8 will be explored.

5.11.3. Immunogenicity and Safety and Efficacy

Association of ADA with safety events may be explored with a primary focus on the following safety events during the TEAE period:

- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Association of treatment emergent and persistent ADA responses and impact on selected efficacy endpoints (ie proportion of patients with IGA 0 or 1, proportion of patients with EASI-75, percent change in EASI score) may be explored (e.g. scatter plot or spaghetti plot).

These above mentioned safety and efficacy analyses will be conducted using the following ADA response categories:

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points
- Patients with persistent ADA response,
- NAb positive patients, that is patients who had positive in the NAb assay at any time point analyzed.
- Peak post-baseline titer level in treatment emergent or treatment boosted ADA positive patients:
  - High,
  - Moderate,
  - Low

5.12. Analyses of Biomarkers

5.12.1. Analyses of Biomarkers

Descriptive statistics for the observed values, change and percent change from Day 1 of current study, change and percent change from baseline of parent study by visit will be summarized for all patients in SAF. It will be provided for the following biomarker variables:

- TARC
- total serum IgE
- hs-CRP,
- anti-TPO

Corresponding figures will be provided.

Correlation of baseline TARC (measured value) and baseline IgE (measured value) of current study with the following categorical clinical endpoints at each visit will be explored for patients without prior experience to dupilumab in the parent studies (i.e. dupilumab naïve patients). Subgroup analysis of these endpoints by baseline value tertiles (<=33rd percentile, <33 - <=67th percentile , >67th percentile) will be provided.

- IGA 0-1
- EASI-75 relative to baseline of current study
- Proportion of patients with improvement (reduction) of pruritus NRS ≥4 from baseline of current study
- Proportion of patients with improvement (reduction) of pruritus NRS ≥3 from baseline of current study

Correlation of baseline TARC (measured value) and IgE (measured value) of current study with the following continuous clinical endpoints will be explored using the Spearman's rho test for patients without prior experience to dupilumab in the parent studies (i.e. dupilumab naïve patients). Both Spearman correlation coefficients and p-value will be reported.

- Percent change from Day 1 of current study in EASI score
- Percent change from Day 1 of current study in weekly pruritus NRS

Shift tables from baselines status to post-baseline status for ANA, anti-TPO and anti-dsDNA will be provided.

All above analyses will be performed on the SAF for all observed data. No missing data will be imputed.

5.12.2. "Normalization" Biomarker Data Related Evaluations

The additional analysis will be performed on the following biomarkers to evaluate the proportion of patients for whom biomarker concentrations "normalize" (shift from above normal to within the normal range) at each visit.

- Total IgE
- TARC

These evaluations will be done using two subsets of the SAF specifically defined as below:

- Include patients with the elevated total IgE, or TARC at baseline of current study. Patients in SAF with a normal (below the ULN) serum biomarker level at Day 1 of current study will be excluded from the analysis for that biomarker, and
- Include patients with the elevated total IgE, or TARC at baseline of parent study. Patients in SAF with a normal (below the ULN) serum biomarker level at baseline of parent study will be excluded from the analysis for that biomarker, and

These patients should also have at least one post-Day 1 of current study measurement and received treatment.

Therefore, the analysis population for each of the biomarkers of interest will vary depending on the number of SAF patients meeting "elevation" criteria at baseline. All observed biomarker data without imputation for missing value will be used for this analysis. Summary tables with normal/elevated status for total IgE, and TARC at baseline and each post-baseline visit (until end-of-study) will be provided.

Method for Determining a ULN for Total IgE

Total IgE 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 AB 2014) are specified in below table, from the product inserts provided by the manufacturer of the assays.

Allergen (Analyte)	Phadia Code	Catalog #	Reference Range
Allergen Total IgE		14-4509-01	0-119 kU/L for both adult sexes

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 3. 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 3 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 3: 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)**

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the first administration of study drug in the current study. The following rules specify the determination by both date/time information:

1. For the AE, lab (including biomarker), PK and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.

2. For other data except AE, lab (including biomarker), PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

The baseline value of parent study is defined as the baseline value a patient had prior to the first dose in the parent study. For patients who have been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416), but could not be randomized because of randomization closure, the initial baseline value of the parent study will be the last nonmissing value during the screening period in the parent study.

6.2. General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data are below the lower limit of quantification (LLOQ) / limit of linearity, then half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAE. For example, if the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to inline with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of follow up date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.4. Analysis Visit Window

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG) will be summarized by the study scheduled visits described in the study protocol and SAP, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination (ET) visit and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit window mapping will be applied for the PK and ADA data.

Under protocol amendment 6, the planned study duration was up to three years or until dupilumab became commercially available in the geographic region of the patient. Protocol amendment 7 was adopted in order to permit those patients in France, Germany Poland and Japan who had already completed three years of treatment to either continue or re-start treatment through 31 December 2017. Patients who were in the safety follow-up period were permitted to resume treatment. Patients who had an End of Study visit were permitted to re-enter the study after being re-consented. Patients who had completed 3 years of treatment resumed treatment in a newly created series of visits called the "treatment extension" period. All patients were scheduled to have an End of Treatment visit on or around 31 December 2017.

Protocol amendment 8 extended the treatment period for up to 5 years for patients in Poland and Finland and to September 2018 in France. Again, patients who had previously had an End of Treatment visit under Amendment 7 and were in the safety follow-up period were permitted to resume treatment. Patients who had an End of Study visit were permitted to re-enter the study after being re-consented.

As a consequence of these two amendments, certain patients from these countries experienced gaps in treatment. One gap occurred between the Amendment 6 EoT date and resumption of treatment under Amendment 7. In addition, patients from Poland experienced a second treatment gap from the EoT date under Amendment 7 and resumption of treatment under Amendment 8.

The data collected at the scheduled visits under protocol amendment 7 and protocol amendment 8 for patients from these countries was collected outside of previously defined visit windows. Hence the analysis visit window will be done separately for data collected under protocol amendment 7/8 for patients from France, Germany, Poland, Japan and Finland and all remaining data. **All remaining data** consists of:

- data collected up to protocol amendment 6 for patients from France, Germany, Poland, Japan and Finland
- data from all other countries

Analysis visit window mapping for all remaining data

No analysis visit windows will be applied for the study scheduled visits except unscheduled visits, early termination visit, the end of treatment/ end of study visits, which are V30 (week 148), V25 (week 112) and V25 (week 108) for patients from UK, V31 (week 164) and V31 (week 160) for all countries except UK.

The following analysis visit windows will be used to map the unscheduled visits, early termination, end of treatment/ end of study visits, based on the study day:

Visit	Target Day	Analysis Visit Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 1	8	[2,11]
Week 2	15	[12,18]
Week 3	22	[19, 25]
Week 4	29	[26, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127]
Week 20	141	[128, 155]
Week 24	169	[156, 183]
Week 28	197	[184, 211]
Week 32	225	[212, 239]
Week 36	253	[240, 267]
Week 40	281	[268, 295]
Week 44	309	[296, 323]
Week 48	337	[324, 351]
Week 52	365	[352, 393]

Visit	Target Day	Analysis Visit Window Based on Study day*
Week 60	421	[394, 449]
Week 68	477	[450, 505]
Week 76	533	[506, 561]
Week 84	589	[562, 617]
Week 92	645	[618, 673]
Week 100	701	[674, 729]
Week 108	757	[730, 785]
Week 116	813	[786, 841]
Week 124	869	[842, 897]
Week 132	925	[898, 953]
Week 140	981	[954, 1009]
Week 148	1037	[1010, 1093]
End of study	1149	>=1094
	785 for UK	>=730

*study day is calculated relative to the date of first study drug injection.

Analysis visit window mapping for data collected under protocol amendment 7/8 for patients from France, Germany, Poland, Japan and Finland

Analysis visit windows will be applied to map all study scheduled visits except extension end of study visit or end of study visit under protocol amendment 7 or 8, based on the study day. Data collected at extension end of study visit or end of study visit under protocol amendment 7 or 8 will be summarized using the nominal visit (i.e. extension end of study visit or end of study visit).

Visit	Target Day	Analysis Visit Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 1	8	[2,11]
Week 2	15	[12,18]
Week 3	22	[19, 25]
Week 4	29	[26, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127]
Week 20	141	[128, 155]

Visit	Target Day	Analysis Visit Window Based on Study day*
Week 24	169	[156, 183]
Week 28	197	[184, 211]
Week 32	225	[212, 239]
Week 36	253	[240, 267]
Week 40	281	[268, 295]
Week 44	309	[296, 323]
Week 48	337	[324, 351]
Week 52	365	[352, 393]
Week 60	421	[394, 449]
Week 68	477	[450, 505]
Week 76	533	[506, 561]
Week 84	589	[562, 617]
Week 92	645	[618, 673]
Week 100	701	[674, 729]
Week 108	757	[730, 785]
Week 116	813	[786, 841]
Week 124	869	[842, 897]
Week 132	925	[898, 953]
Week 140	981	[954, 1009]
Week 148	1037	[1010, 1065]
Week 156	1093	[1066, 1149]
Week 172	1205	[1150, 1261]
Week 188	1317	[1262, 1373]
Week 204	1429	[1374, 1485]
Week 220	1541	[1486, 1597]
Week 236	1653	[1598, 1709]
Week 252	1765	[1710, 1793]
End of study	1821	>=1794

*study day is calculated relative to the date of first study drug 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.

Analysis visit window mapping for weekly pruritus NRS

For the weekly pruritus NRS collected via IVRS, the following analysis visit windows will be used based on the study day:

Visit	Target Day	Analysis Visit Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 1	8	[2,11]
Week 2	15	[12,18]
Week 3	22	[19, 25]
Week 4	29	[26, 32]
Week 5	36	[33, 39]
Week 6 onwards (every week)	43 (every 7 days)	….

* study day is calculated relative to the date of first study drug injection.

If there are multiple patient reported NRSs in the same week, then the average value of all scores in the week will be used for analysis.

Analysis visit window mapping for Ophthalmological Examination

No analysis visit windows will be applied for the ophthalmological exam scheduled visits in the sub-study. Data will be summarized using the nominal visit.

7. INTERIM ANALYSIS

This is an open-label extension study. No formal interim analyses will be planned for this study.

A first step analysis was performed to support the submission of market application for dupilumab in AD indication in third quarter of year 2016. All data prior to the cutoff date (11Apr2016) were included in this analysis. The process to derive the data cut-off for the first step analysis is outlined in Appendix 10.7.

A second step analysis will be performed in first quarter of year 2019 in order to have long term data of dupilumab in AD indication. All data prior to the cutoff date (around 01Dec2018) for patients in Poland, Finland, Russia, New Zealand, Singapore and all data for patients from remaining countries will be included in this analysis. Patients from remaining countries will either complete or early withdrawn from the study at time of database lock. The process to derive the data cut-off for the second step analysis is outlined in Appendix 10.8.

Future analyses will be performed to support the subsequent regulatory filings. The details and data cutoff date will be specified in future SAP addendum.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 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.

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.

Greiner W, Claes C, Buschbach JJV, Graf von der Schulenburg JM. Validating the EQ-5D with time trade-off for the German population. Eur J Health Econ 2005; 6(2):124-130.

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.

ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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.

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

10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive Statistical Method	Subgroup Analysis	Other Analyses
Continuous variables	SAF	Descriptive Statistics	No	Yes for key secondary endpoint	No
Categorical variables	SAF	Descriptive Statistics	No	Yes for key secondary endpoint	No
Time to event variable	SAF	Kaplan-Meier curve	No	No	No

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive Statistics	No	Yes for selected AEs	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

Study assessments and procedures for protocol amendment 7 global are presented by study period and visit in Table 4.

Table 4: Schedule of Events – Visits 1 through 8 (Week 12)

Study Procedures	**Screening***	**Baseline**	**Treatment Period**					
Visit (V)	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**
Week (Wk)			**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**
Day (D)	**-28 to -1** [a]	**D 1**	**D 8**	**D 15**	**D 22**	**D 29**	**D 57**	**D 85**
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Screening/Baseline:								
Informed consent	X							
Inclusion/Exclusion	X	X						
Medical History/Demographics	X	X						
Training on IVRS/IWRS		X						
Treatment:								
Injection training/observation		X				X		
Administer study drug[c]		X[b]						
Patient dosing diary [d]		X				X		X
Study drug dispensation/account.[e]		X				X		X
Con meds/procedures	X	X				X		

Study Procedures	**Screening***	**Baseline**	**Treatment Period**					
Visit (V)	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**
Week (Wk)			**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**
Day (D)	**-28 to -1** [a]	**D 1**	**D 8**	**D 15**	**D 22**	**D 29**	**D 57**	**D 85**
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Efficacy: [f]								
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[i]		X				X		
IGA, EASI	X	X				X		
POEM, DLQI, EQ-5D [g]		X						
Safety: [f]								
Weight	X	X						
Height	X	X						
Vital signs	X	X				X		
Physical examination		X						
Ophthalmology exam[k] (select sites and patients)		X				X		X
Adverse events[h]	X	X				X		X
Laboratory Testing: [f]								
Hematology, Chemistry	X	X						
Pregnancy test, WOCBP only	Serum	Urine[l]				Urine[l]		Urine[l]
HIV screening [j]	X							
HBsAg, HBcAb, hepatitis C antibody[j]	X							

Study Procedures	**Screening***	**Baseline**	**Treatment Period**					
Visit (V)	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**
Week (Wk)			**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**
Day (D)	**-28 to -1** [a]	**D 1**	**D 8**	**D 15**	**D 22**	**D 29**	**D 57**	**D 85**
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Drug Concentration/PK and Anti-drug Antibody Testing: [f]								
Drug concentration/PK sample		X						
ADA sample		X						

*Note: The screening visit in this study may coincide with the last visit in the previous study. Assessments that are common to both studies will be performed only once.

a. Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.

b. A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8. In addition to the predose assessments, vital signs and AEs will be assessed at 30 (+/- 10) minutes postdose.

c. Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).

d. If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic

e. Starting at visit 2, study drug will be dispensed to the patient for all doses that will be administered before the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

f. To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.

g. The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.

h. In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

i. Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

j. Any of these tests is required only for patients who have not had a documented negative result for the respective test within 1 year prior to baseline (the negative HIV result must be from a parent study).

k. An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit, which can take place at any time between the screening and baseline visits, inclusive.

l. Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.

Table 5: Schedule of Events – Visits 9 (Week 16) through 18 (Week 52)

Study Procedures	**Treatment Period**									
Visit (V)	**V 9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**
Week (Wk)	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Day (D)	**D 113**	**D 141**	**D 169**	**D 197**	**D 225**	**D 253**	**D 281**	**D 309**	**D 337**	**D 365**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:										
Administer study drug [a]	X									
Patient dosing diary[b]	X		X		X		X		X	X
Study drug dispensation/account.[c]	X		X		X		X		X	X
Con meds/procedures	X				X				X	
Efficacy: [d]										
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[g]	X								X	
IGA, EASI	X								X	
POEM, DLQI, EQ-5D [e]									X	
Safety: [d]										
Weight									X	
Vital signs	X				X				X	
Ophthalmology exam[i] (select sites and patients)	X				X				X	
Adverse events[f]	X		X		X		X			X

Study Procedures	**Treatment Period**									
Visit (V)	**V 9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**
Week (Wk)	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Day (D)	**D 113**	**D 141**	**D 169**	**D 197**	**D 225**	**D 253**	**D 281**	**D 309**	**D 337**	**D 365**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Laboratory Testing: [d]										
Hematology, Chemistry	X								X	
Pregnancy test, WOCBP only	Urine[h], monthly throughout the study treatment									
Drug Concentration and Antibody Testing: [d]										
Drug Concentration sample									X	
ADA sample									X	

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c.] Study drug will be dispensed to the patient for all doses that will be administered before the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[d.] To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.
[e.] The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.
[f.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[g.] Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[h.] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[i.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.

Table 6: Schedule of Events – Visits 19 (Week 60) through 24 (Week 100)

Study Procedures	**Treatment Period**					
Visit (V)	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**
Week (Wk)	**Wk 60**	**Wk 68**	**Wk 76**	**Wk 84**	**Wk 92**	**Wk 100**
Day (D)	**D 421**	**D 477**	**D 533**	**D 589**	**D 645**	**D 701**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:						
Administer study drug[a]	X					
Patient dosing diary[b]	X	X	X	X	X	X
Study drug dispensation/account.[c]	X	X	X	X	X	X
Con meds/procedures	X		X		X	
Efficacy: [d]						
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[g]	X					X
IGA, EASI	X					X
POEM, DLQI, EQ-5D [e]						X
Safety: [d]						
Weight	X		X			X
Vital signs	X		X	X	X	X
Ophthalmology exam[i] (select sites and patients)	X		X		X	
Adverse events[f]	X	X	X	X	X	X

Study Procedures	**Treatment Period**					
Visit (V)	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**
Week (Wk)	**Wk 60**	**Wk 68**	**Wk 76**	**Wk 84**	**Wk 92**	**Wk 100**
Day (D)	**D 421**	**D 477**	**D 533**	**D 589**	**D 645**	**D 701**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Laboratory Testing: [d]						
Hematology, Chemistry						X
Pregnancy test, WOCBP only	Urine[h], monthly throughout the study treatment					
Drug Concentration and Antibody Testing: [d]						
Drug Concentration sample						X
ADA sample						X

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c.] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug vials at each clinic visit.
[d.] To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.
[e.] The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.
[f.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[g.] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[h.] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[i.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit

Table 7: Schedule of Events – Visits 25 (Week 108) through End of Study (Week 160)

Study Procedures	**Treatment Period**					**End of Tx**	**End of Study[m]**	**Early Termination**	**Unscheduled Visit[j]** (if applicable)
Visit (V)	**V 25**	**V 26**	**V 27**	**V 28**	**V 29**	**V30**	**V31**		
Week (Wk)	**Wk 108**	**Wk 116**	**Wk 124**	**Wk 132**	**Wk 140**	**Wk 148**	**Wk160 or last dose +12Wk**		
Day (D)	**D 757**	**D 813**	**D 869**	**D 925**	**D 981**	**D 1037**	**D1121 or Last dose +84D**		
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d			
Treatment:									
Administer study drug[a]	X								
Patient dosing diary[b]	X	X	X	X	X	X		X	
Study drug dispensation/account.[c]	X	X	X	X	X	X		X	
Con meds/procedures	X		X		X		X	X	X
Efficacy: [d]									
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	X		X				X	X[f]	X[h]
IGA, EASI			X				X	X	X
Safety: [d]									
Weight	X		X			X	X	X	X
Vital signs	X		X		X	X	X	X	X
Ophthalmology exam[k] (select sites and patients)	X		X		X		X		X[l]
Adverse events[e]	X	X	X	X	X	X	X	X	X

Study Procedures	Treatment Period					End of Tx	End of Study[m]	Early Termination	Unscheduled Visit[j] (if applicable)
Visit (V)	**V 25**	**V 26**	**V 27**	**V 28**	**V 29**	**V30**	**V31**		
Week (Wk)	**Wk 108**	**Wk 116**	**Wk 124**	**Wk 132**	**Wk 140**	**Wk 148**	**Wk160 or last dose +12Wk**		
Day (D)	**D 757**	**D 813**	**D 869**	**D 925**	**D 981**	**D 1037**	**D1121 or Last dose +84D**		
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d			
Laboratory Testing: [d]									
Hematology, Chemistry						X			X
Pregnancy test, WOCBP only	Urine[g], monthly throughout the study treatment								Urine
HIV screening									X
HBsAg, HBcAb, hepatitis C antibody									X
Drug Concentration and Antibody Testing: [d]									
Drug Concentration sample			X				X	X	X
ADA sample			X			X	X[i]	X[i]	X

[a] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug vials at each clinic visit.
[d] To be collected before the injection of study drug.
[e] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[f] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[g] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[h] If the call was performed on the patient's weekly schedule, then it will not need to be repeated.
[i] Patients who test positive for ADA at their last study visit (early termination visit or end of study visit) may be asked to return to the clinic to have additional ADA samples collected for analysis.
[j] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.

[k] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.
[l] Patients who experience AEs consistent with conjunctivitis or other superficial inflammation of the eye (blepharitis, keratitis, etc) should undergo additional (unscheduled) ophthalmology exams to allow accurate diagnosis and adequate treatment.
[m] If the end of study assessments cannot be completed on the scheduled date (ie, 12 weeks after the last dose of dupilumab), a late visit is acceptable and is preferable to foregoing these assessments altogether; this visit should be conducted as close as possible to the scheduled date.

Study assessments and procedures for protocol amendment 8 for Poland/Finland are presented by study period and visit in Table 12, Table 13, and Table 14.

Table 8: Schedule of Events – Visits 1 through 8 (Week 12)

Study Procedures	**Screening***	**Baseline**	**Treatment Period**					
Visit (V)	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**
Week (Wk)			**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**
Day (D)	**-28 to -1** [a]	**D 1**	**D 8**	**D 15**	**D 22**	**D 29**	**D 57**	**D 85**
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Screening/Baseline:								
Informed consent	X							
Inclusion/Exclusion	X	X						
Medical History/Demographics	X	X						
Training on IVRS/IWRS		X						
Treatment:								
Injection training/observation		X				X		
Administer study drug[c]		X[b]						
Patient dosing diary [d]		X				X		X
Study drug dispensation/account.[e]		X				X		X
Con meds/procedures	X	X				X		
Efficacy: [f]								
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[i]		X				X		
IGA, EASI	X	X				X		
POEM, DLQI, EQ-5D [g]		X						

Study Procedures	**Screening***	**Baseline**	**Treatment Period**					
Visit (V)	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**
Week (Wk)			**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**
Day (D)	**-28 to -1** [a]	**D 1**	**D 8**	**D 15**	**D 22**	**D 29**	**D 57**	**D 85**
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Safety: [f]								
Weight	X	X						
Height	X	X						
Vital signs	X	X				X		
Physical examination		X						
Ophthalmology exam[k] (select sites and patients)		X				X		X
Adverse events[h]	X	X				X		X
Laboratory Testing: [f]								
Hematology, Chemistry	X	X						
Pregnancy test, WOCBP only	Serum	Urine[l]				Urine[l]		Urine[l]
HIV screening [j]	X							
HBsAg, HBcAb, hepatitis C antibody [j]	X							

Study Procedures	Screening*	Baseline	Treatment Period					
Visit (V)	V 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8
Week (Wk)			Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12
Day (D)	-28 to -1 [a]	D 1	D 8	D 15	D 22	D 29	D 57	D 85
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Drug Concentration/PK and Anti-drug Antibody Testing: [f]								
Drug concentration/PK sample		X						
ADA sample		X						

*Note: The screening visit in this study may coincide with the last visit in the previous study. Assessments that are common to both studies will be performed only once.

a. Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.
b. A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8. In addition to the predose assessments, vital signs and AEs will be assessed at 30 (+/- 10) minutes postdose.
c. Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
d. If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
e. Starting at visit 2, study drug will be dispensed to the patient for all doses that will be administered before the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
f. To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.
g. The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.
h. In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
i. Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
j. Any of these tests is required only for patients who have not had a documented negative result for the respective test within 1 year prior to baseline (the negative HIV result must be from a parent study).
k. An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit, which can take place at any time between the screening and baseline visits, inclusive.
l. Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.

Table 9: Schedule of Events – Visits 9 (Week 16) through 18 (Week 52)

Study Procedures	**Treatment Period**									
Visit (V)	**V 9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**
Week (Wk)	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Day (D)	**D 113**	**D 141**	**D 169**	**D 197**	**D 225**	**D 253**	**D 281**	**D 309**	**D 337**	**D 365**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:										
Administer study drug [a]	X									
Patient dosing diary[b]	X		X		X		X		X	X
Study drug dispensation/account.[c]	X		X		X		X		X	X
Con meds/procedures	X				X				X	
Efficacy: [d]										
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[g]	X								X	
IGA, EASI	X								X	
POEM, DLQI, EQ-5D [e]									X	
Safety: [d]										
Weight									X	
Vital signs	X				X				X	
Ophthalmology exam[i] (select sites and patients)	X				X				X	
Adverse events[f]	X		X		X		X		X	X

Study Procedures	**Treatment Period**									
Visit (V)	**V 9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**
Week (Wk)	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Day (D)	**D 113**	**D 141**	**D 169**	**D 197**	**D 225**	**D 253**	**D 281**	**D 309**	**D 337**	**D 365**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Laboratory Testing: [d]										
Hematology, Chemistry	X								X	
Pregnancy test, WOCBP only	Urine[h], monthly throughout the study treatment									
Drug Concentration and Antibody Testing: [d]										
Drug Concentration sample									X	
ADA sample									X	

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c.] Study drug will be dispensed to the patient for all doses that will be administered before the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[d.] To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.
[e.] The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.
[f.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[g.] Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[h.] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[i.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.

Table 10: Schedule of Events – Visits 19 (Week 60) through 24 (Week 100)

Study Procedures	**Treatment Period**					
Visit (V)	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**
Week (Wk)	**Wk 60**	**Wk 68**	**Wk 76**	**Wk 84**	**Wk 92**	**Wk 100**
Day (D)	**D 421**	**D 477**	**D 533**	**D 589**	**D 645**	**D 701**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:						
Administer study drug[a]	X					
Patient dosing diary[b]	X	weekly throughout the study treatment				X
Study drug dispensation/account.[c]	X	throughout the study treatment at each visit				X
Con meds/procedures	X		X		X	
Efficacy: [d]						
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[g]	X					X
IGA, EASI	X					X
POEM, DLQI, EQ-5D [e]						X
Safety: [d]						
Weight	X		X			X
Vital signs	X		X	X	X	X
Ophthalmology exam[i] (select sites and patients)	X		X		X	
Adverse events[f]	X	throughout the study				X

Study Procedures	**Treatment Period**					
Visit (V)	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**
Week (Wk)	**Wk 60**	**Wk 68**	**Wk 76**	**Wk 84**	**Wk 92**	**Wk 100**
Day (D)	**D 421**	**D 477**	**D 533**	**D 589**	**D 645**	**D 701**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Laboratory Testing: [d]						
Hematology, Chemistry						X
Pregnancy test, WOCBP only	Urine[h], monthly throughout the study treatment					
Drug Concentration and Antibody Testing: [d]						
Drug Concentration sample						X
ADA sample						X

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c.] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[d.] To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.
[e.] The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.
[f.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[g.] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[h.] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[i.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit

Table 11: Schedule of Events – Visits 25 (Week 108) through Visit 30 (Week 148)

Study Procedures	**Treatment Period**					
Visit (V)	**V 25**	**V 26**	**V 27**	**V 28**	**V 29**	**V30**
Week (Wk)	**Wk 108**	**Wk 116**	**Wk 124**	**Wk 132**	**Wk 140**	**Wk 148**
Day (D)	**D 757**	**D 813**	**D 869**	**D 925**	**D 981**	**D 1037**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:						
Administer study drug[a]	X	weekly throughout the study treatment				X
Patient dosing diary[b]	X	weekly throughout the study treatment				X
Study drug dispensation/account[c]	X	throughout the study treatment at each visit				X
Con meds/procedures	X		X		X	
Efficacy: [d]						
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	X		weekly throughout the study			X
IGA, EASI			X			
Safety: [d]						
Weight	X		X		X	
Vital signs	X		X		X	
Ophthalmology exam[h] (select sites and patients)	X		X		X	
Adverse events[e]	X	throughout the study				X

Study Procedures	**Treatment Period**					
Visit (V)	**V 25**	**V 26**	**V 27**	**V 28**	**V 29**	**V30**
Week (Wk)	**Wk 108**	**Wk 116**	**Wk 124**	**Wk 132**	**Wk 140**	**Wk 148**
Day (D)	**D 757**	**D 813**	**D 869**	**D 925**	**D 981**	**D 1037**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Laboratory Testing: [d]						
Hematology, Chemistry						X
Pregnancy test, WOCBP only[g]	X	Urine monthly throughout the study				X
HIV screening						
HBsAg, HBcAb, hepatitis C antibody						
Drug Concentration and Antibody Testing: [d]						
Drug Concentration sample			X			
ADA sample			X			X

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c.] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[d.] To be collected before the injection of study drug.
[e.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[f.] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[g.] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[h.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.

Table 12: Schedule of Events – Visits 31 (Week 156) through Visit 36 (Week 196)

Study Procedures	**Treatment Period**					
Visit (V)	**V 31**	**V 32**	**V 33**	**V 34**	**V 35**	**V 36**
Week (Wk)	**Wk 156**	**Wk 164**	**Wk 172**	**Wk 180**	**Wk 188**	**Wk 196**
Day (D)	**D 1093**	**D 1149**	**D 1205**	**D 1261**	**D 1317**	**D 1373**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:						
Administer study drug[a]	X	weekly throughout the study treatment				X
Patient dosing diary[b]	X	weekly throughout the study treatment				X
Study drug dispensation/account.[c]	X	throughout the study treatment at each visit				X
Con meds/procedures	X		X		X	
Efficacy: [d]						
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	X	weekly throughout the study				X
IGA, EASI	X					
Safety: [d]						
Weight	X		X		X	
Vital signs	X		X		X	
Ophthalmology exam[h] (select sites and patients)	X		X		X	
Adverse events[e]	X	throughout the study				X

Study Procedures	**Treatment Period**					
Visit (V)	**V 31**	**V 32**	**V 33**	**V 34**	**V 35**	**V 36**
Week (Wk)	**Wk 156**	**Wk 164**	**Wk 172**	**Wk 180**	**Wk 188**	**Wk 196**
Day (D)	**D 1093**	**D 1149**	**D 1205**	**D 1261**	**D 1317**	**D 1373**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Laboratory Testing: [d]						
Hematology, Chemistry						
Pregnancy test, WOCBP only[g]	Urine	Urine monthly throughout the study				
HIV Screening						
HBsAg, HBcAb, hepatitis C antibody						
Drug Concentration and Antibody Testing: [d]						
Drug Concentration sample						
ADA sample			X			

[a] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[d] To be collected before the injection of study drug.
[e] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[f] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[g] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[h] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit

Table 13: Schedule of Events – Visits 37 (Week 204) through Visit 43 (Week 252)

Study Procedures	**Treatment Period**						
Visit (V)	**V 37**	**V 38**	**V 39**	**V 40**	**V 41**	**V 42**	**V 43**
Week (Wk)	**Wk 204**	**Wk 212**	**Wk 220**	**Wk 228**	**Wk 236**	**Wk 244**	**Wk 252**
Day (D)	**D 1429**	**D 1485**	**D 1541**	**D 1597**	**D 1653**	**D 1709**	**D 1765**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:							
Administer study drug[a]	X	weekly throughout the study treatment					X
Patient dosing diary[b]	X	weekly throughout the study treatment					X
Study drug dispensation/account.[c]	X	throughout the study treatment at each visit					X
Con meds/procedures	X		X		X		X
Efficacy: [d]							
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	X	weekly throughout the study					X
IGA, EASI	X						
Safety: [d]							
Weight	X		X		X		X
Vital signs	X		X		X		X
Ophthalmology exam[h] (select sites and patients)	X		X		X		X
Adverse events[e]	X	throughout the study					X

Study Procedures	**Treatment Period**						
Visit (V)	**V 37**	**V 38**	**V 39**	**V 40**	**V 41**	**V 42**	**V 43**
Week (Wk)	**Wk 204**	**Wk 212**	**Wk 220**	**Wk 228**	**Wk 236**	**Wk 244**	**Wk 252**
Day (D)	**D 1429**	**D 1485**	**D 1541**	**D 1597**	**D 1653**	**D 1709**	**D 1765**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Laboratory Testing: [d]							
Hematology, Chemistry	X						
Pregnancy test, WOCBP only[g]	X		Urine Monthly throughout study				
HIV Screening							
HBsAg, HBcAb, hepatitis C antibody							
Drug Concentration and Antibody Testing: [d]							
Drug Concentration sample							
ADA sample			X				

[a] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[d] To be collected before the injection of study drug.
[e] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
f Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[g] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[h] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit

Table 14: Schedule of Events – End of Treatment, End of Study, Early Termination, Unscheduled Visit, and Re-entry Visit

Study Procedures	**End of Treatment**	**End of Study[m]**	**Early Termination**	**Unscheduled Visit[j]** (if applicable)	**Re-entry Visit[r]** (for patients who re-enter the study)
Visit (V)	**V 44**				
Week (Wk)	**260**	**Last dose +12Wk**			
Day (D) Visit Window (d)	**D 1821** +/-3d	**Last dose +84D** +/-30d			
Treatment:					
Inclusion/Exclusion (Re-entry)					X
Informed Consent (Re-entry)					X
Demographics (Re-entry)					X
Administer study drug[a]	X				
Patient dosing diary[b]	X		X		
Study drug dispensation/account[c]	X[n]		X	X	
Con meds/procedures	X	X	X	X	X
Efficacy: [d]					
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]			X[f]	X[h]	
IGA, EASI	X	X	X	X	

Study Procedures	**End of Treatment**	**End of Study**[m]	**Early Termination**	**Unscheduled Visit**[j] (if applicable)	**Re-entry Visit**[r] (for patients who re-enter the study)
Visit (V)	**V 44**				
Week (Wk)	**260**	**Last dose +12Wk**			
Day (D) Visit Window (d)	**D 1821** +/-3d	**Last dose +84D** +/-30d			
Safety: [d]					
Weight	X	X	X	X	
Vital signs	X	X	X	X	
Ophthalmology exam[k] (select sites and patients)		X		X[l]	
Adverse events[e]	X	X	X	X	X
Laboratory Testing: [d]					
Hematology, Chemistry	X			X	X[o]
Pregnancy test, WOCBP only[g]	Urine Monthly			X	Serum[p]
HIV screening				X	X[q]
HBsAg, HBcAb, hepatitis C antibody				X	X[q]

Study Procedures	**End of Treatment**	**End of Study**[m]	**Early Termination**	**Unscheduled Visit**[j] (if applicable)	**Re-entry Visit**[r] (for patients who re-enter the study)
Visit (V)	**V 44**				
Week (Wk)	**260**	**Last dose +12Wk**			
Day (D)	**D 1821**	**Last dose +84D**			
Visit Window (d)	+/-3d	+/-30d			
Drug Concentration and Antibody Testing: [d]					
Drug Concentration sample	X	X	X	X	
ADA sample	X	X[i]	X[i]	X	

[a] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[b] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[c] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[d] To be collected before the injection of study drug.
[e] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.
[f] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[g] Patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site.
[h] If the call was performed on the patient's weekly schedule, then it will not need to be repeated.
[i] Patients who test positive for ADA at their last study visit (early termination visit or end of study visit) may be asked to return to the clinic to have additional ADA samples collected for analysis.
[j] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.
[k] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.
[l] Patients who experience AEs consistent with conjunctivitis or other superficial inflammation of the eye (blepharitis, keratitis, etc) should undergo additional (unscheduled) ophthalmology exams to allow accurate diagnosis and adequate treatment.
[m] .If the end of study assessments cannot be completed on the scheduled date (ie, 12 weeks after the last dose of dupilumab), a late visit is acceptable and is preferable to foregoing these assessments altogether; this visit should be conducted as close as possible to the scheduled date.
[n] Only study drug accountability takes place at this visit.
[o] Sample will be collected only if the last sample was not collected within 12 months.

[p] Serum pregnancy test must be negative before dosing.
[q] Testing is required at re-entry for patients who have not been tested within 12 months prior to re-entry.
[r] Patients who have completed the End of Study visit as per amendment 7 and who are eligible to resume treatment may re-enter the trial at the next scheduled visit they would have attended if they had not completed the study; the next visit should be scheduled within 7 days of the re-entry visit. Patients are not eligible to re-enter the trial if more than 12 weeks have elapsed since their End of Study visit.

10.3. Criteria for Treatment-Emergent Potentially Clinical Significant Value

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided

Parameter	Treatment Emergent PCSV	Comments
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.

Parameter	Treatment Emergent PCSV	Comments
Glucose		
Hypoglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black);	Increase in WBC: not relevant.
	<2.0 Giga/L and >=2.0 Giga/L at baseline (Black)	
	≥16.0 Giga/L and < 16 Giga/L at baseline	To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black);	International Consensus meeting on drug-induced blood cytopenias, 1991.
	<1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female.	Three criteria are independent.
	≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
	Decrease from Baseline ≥20 g/L	
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male; ≤0.32 v/v and > 0.32 v/v at baseline forFemale	Two Criteria are independent
	≥0.55 v/v and < 0.55 v/v at baseline for Male; ≥0.5 v/v and < 0.5 v/v at baseline for Female	

Parameter	Treatment Emergent PCSV	Comments
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	

Parameter	Treatment Emergent PCSV	Comments
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. 5 independent criteria

10.4. SAS code for EQ-5D index utility scoring

```
/*=================================================================*/;
/*  Aim                       : Derive the EQ5-D index (utility)           */;
/*  Source for the algorithm : scoring EQ-5D health states (Rosalind Rabin */;
/*            (cf. G:\_HE\PRO questionnaire\EQ5D\scoring\YorkTariffx.doc)  */;
/*  Note                      : UK based population (Dolan, 1997)          */;
/*  Author                    : Elisheva Smadja                            */;
/*=================================================================*/;

data EUROQOL;   set temp;
   profil= (10000*eqq1cd)+(1000*eqq2cd)+(100*eqq3cd)+(10*eqq4cd)+eqq5cd;
   eq5d=1;
**********Mobility********;
if eqq1cd=2     then eq5d=eq5d-0.069;
if eqq1cd=3     then eq5d=eq5d-0.314;
********Self-care**********;
if eqq2cd=2     then eq5d=eq5d-0.104;
if eqq2cd=3     then eq5d=eq5d-0.214;
******Usual activities*****;
if eqq3cd=2     then eq5d=eq5d-0.036;
if eqq3cd=3     then eq5d=eq5d-0.094;
*****Pain/discomfort******;
if eqq4cd=2     then eq5d=eq5d-0.123;
if eqq4cd=3     then eq5d=eq5d-0.386;
*****Anxiety/depression*****;
if eqq5cd=2     then eq5d=eq5d-0.071;
if eqq5cd=3     then eq5d=eq5d-0.236;

if (eqq1cd ne 1 or eqq2cd ne 1 or eqq3cd ne 1 or eqq4cd ne 1 or eqq5cd ne 1)
                then eq5d=eq5d-0.081;
if (eqq1cd=3 or eqq2cd=3 or eqq3cd=3 or eqq4cd=3 or eqq5cd=3)
                then eq5d=eq5d-0.269;
if (eqq1cd=. or eqq2cd=. or eqq3cd=. or eqq4cd=. or eqq5cd=.)
                then eq5d=.;
run;
```

10.5. Exposure-Adjusted Analyses

To account for potentially differential exposure time, two types of exposure-adjusted analyses will be provided for analysis, namely, number of events per 100 patient-years and number of patients with at least one event per 100 patient-years.

Number of events per 100 patient-years

The number of events per 100 patient-years (NEPY) will be calculated as the number of events occurring in the population divided by the sum of the exposure over all patients (ie, total exposure) in the TEAE period.

$$NEPY = 100 \times \frac{\sum n_i}{\sum t_i}$$

where n_i is the number of events observed for patient i; t_i is total TEAE exposure for patient i in person-year unit.

Number of patients with at least one event per 100 patient-years

The exposure-adjusted incidence rate (EAIR) is the expected number of patients with at least one specific adverse event per 100 patients taking the treatment for 1 year (52 weeks). The number of patients with at least one event per 100 patient-years will be calculated as the number of patients having a specific event divided by the total person-year among patients in the pool and at risk of an initial occurrence of the event. In particular, the EAIR is computed as follows:

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

where n is the number of patients with the specific adverse event; it is a patient's exposure time in person-year unit. For each of the adverse events of interest, the exposure time 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.

10.6. Search Criteria for TEAE of Special Interest/TEAE Syndrome

Below table is the search criteria for AESI under protocol amendment 4 and 5.

AESI	Search Criteria
Anaphylactic reactions	Narrow SMQ for "anaphylactic reaction"
Acute allergic reactions that require treatment	Narrow SMQ for "hypersensitivity" Action taken for AE="medication" or "surgery" *Note: Blinded manual adjudication of relevant PTs will be required by the study medical monitor, before database locks*
Severe ISRs that last longer than 24 hours	-HLT = Injection site reactions - Severity = "severe" - duration of AE > 24 hours
Mycosis fungoides or other forms of cutaneous T cell lymphoma	-HLT = "Mycosis fungoides" • Includes LLT = Sezary syndrome • Includes LLT = Cutaneous T-cell lymphoma -PT = "Cutaneous T-cell dyscrasia
Any severe infection	-SOC = Infections and infestations -Severity = "severe
Any infection requiring treatment with parenteral antibiotics	-SOC = Infection and infestations -Action taken for AE = "medication" -ConMed: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = IV, IM
Any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks	-SOC = Infection and infestations -Action taken for AE = "medication" -Check CM: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = PO and Treatment duration >14 days
Any clinical endoparasitosis	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection

AESI	Search Criteria
Any opportunistic infection[a]	The following HLTs plus PTs -HLT = Pneumocystis infection -HLT* = Fungal infections NEC -HLT* = Pseudallescheria infections -HLT = Herpes viral infections -HLT = Paracoccidioides infections -HLT = Sporothrix infections -HLT = Cryptosporidia infections -HLT* = Trypanosomal infections -HLT* = Campylobacter infections -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 -Eczema herpeticum

AESI	Search Criteria
	-Kaposi's varicelliform eruption -Herpes zoster Note: *Blinded manual adjudication of relevant PTs under each of HLTs listed above will be required by the study medical monitor, before database locks
Suicidal behavior	Include the following PTs -Completed suicide -Suicidal ideation -Suicide attempt -Depression suicidal -Suicidal behavior

[a] The definition of opportunistic infections is referring to the recent consensus guidance for opportunistic infections in the setting of biologic therapy (K L Winthrop et al, 2015)

Below table is the search criteria for AESI under protocol amendment 6/7/8.

AESI	Search Criteria
Anaphylactic reactions	For SMQ "anaphylactic reaction" An **algorithmic approach** will be used. A case must include either: 4. A narrow term (a term from Category **A**); 5. Patient with both a term from Category **B** AND a term from Category **C**; 6. Patient with a term from Category **D** AND { a term from Category **B** - OR a term from Category **C** } For bullets 2 and 3, the search terms that are included under the SMQ for a particular event need to have the same start date (for e.g. if search shows cough (category B term) occurring at day 3 and urticaria (category C term) occurring at day 7, this event is not adjudicated as anaphylactic reaction as this is inconsistent with the clinical presentation of anaphylaxis as an acute event with simultaneous involvement of 2 or more body systems. Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock

AESI	Search Criteria
Systemic or severe hypersensitivity reactions	Hypersensitivity: Narrow SMQ for hypersensitivity excluding preferred term equal to dermatitis atopic or eczema For systemic hypersensitivity, events in which 2 or more body systems are involved (as defined by System Organ Class) would be considered for adjudication based on further medical judgement For severe hypersensitivity, an additional search will be done; – HLT = Injection site reactions – Severity = "severe" Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Malignancy	• SMQ "Malignant tumours" • SMQ "Tumours of unspecified malignancy"
Helminthic infections	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection
Suicidal behavior	Include the following PTs • Completed suicide • Suicidal ideation • Suicide attempt • Depression suicidal • Suicidal behavior
Any type of conjunctivitis or blepharitis or keratitis (only events that are either severe or serious)	broad CMQ conjunctivitis (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, Ocular hyperaemia, Conjunctival hyperaemia, Xerophthalmia); Blepharitis PTs (Blepharitis, blepharitis allergic); Keratitis PTs (Keratitis, Allergic keratitis, Ulcerative keratitis, Atopic keratoconjunctivitis, Herpes ophthalmic, Ophthalmic herpes simplex); **AND** • Serious AE= "Yes" OR Severity= "severe" Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.

[1] The search criteria are meant to assist the process of identification of TEAE of Special Interest/TEAE Syndrome. However, since these criteria might not be exhaustive in some cases or may not be specific in other cases. Hence an additional review of all PTs in the database may be performed by the Medical monitor, based on medical judgement, to identify any TEAE of Special Interest/TEAE Syndrome that might have been missed by the criteria or to identify any TEAE may been inaccurately assigned as AESI by the algorithmic search

10.7. Process to Derive Data Cut-off for the First Step Analysis

Database lock of the first step analysis for R668-AD-1225 study is planned for 05-May-2016 with data cut-off date 11-Apr-2016.

The data cutoff algorithm will be applied to the raw datasets extracted from Electronic Data Capture (EDC) and IVRS system.

I. Patients to be included for the first step analysis

1. Include enrolled patients with date of enrollment <=11Apr2016 inside ELIG1 raw dataset.

2. Include screen failure patients with record date <=11Apr2016 inside ELIG raw dataset.

Note: only these patients' data will be included in the first step analysis. Hence patients who are under screening and do not enroll prior to the data cut-off date will not be included in the first step analysis.

II. Data recorded during the screening period:

The following data recorded during the screening period for patients identified in step (I) do not need data cut-off. All data for patients identified in step (I) included in the final locked data transfer will be used for the first step analysis.

Informed consent

Inclusion/exclusion

Medical history

Demographics

Previous AD study information

III. Data collected through IVRS

1. All diary data collected on or before 11-Apr-2016 will be kept for the first step analysis.

2. For the kit allocation dataset, all records will be kept for the first step analysis.

IV. Visit dependent data:

All visit dependent data on or before 11-Apr-2016 will be kept for the first step analysis. All visit dependent data collected later than 11-Apr-2016 will not be included in the first step analysis datasets. Unscheduled visits with a date on or before 11-Apr-2016 will be kept on the first step analysis.

V. Visit independent/Event based data:

This includes adverse events, concomitant/prior medication and procedure:

All event records with a start date later than 11-Apr-2016 will be censored (this includes incomplete dates when the incomplete date is without any doubts later than 11-Apr-2016, e.g. the incomplete date is May 2016).

Records with a start date earlier or on 11-Apr-2016 will be kept (this includes incomplete dates when the incomplete date is earlier than 11-Apr-2016 or in case of doubts, e.g. the incomplete date for an event is April 2016, or only year 2016 or even a missing date).

For the events included in the first step analysis cut-off, several adaptions to the data will be made:

- Adverse Events:
  - If a stop date of adverse event is specified and earlier or equal to 11-Apr-2016 then the record will not be changed.
  - If a stop date of adverse event is specified and later than 11-Apr-2016, then the stop date will be deleted (set to missing) and the outcome of the adverse event (SAS variable AEOUT/AEOUTN) will be set to missing, AE ongoing status will be set to Yes.
  - If no stop date is specified and the outcome is either not yet reported (AEOUT/AEOUTN is blank) or is reported (AEOUT in (recovering/resolving, not recovered/not resolved, unknown)), then the outcome will be set to missing (AEOUT/AEOUTN is blank)
- Concomitant medication/procedure:
  - If a stop date is reported which is earlier than or on 11-Apr-2016, the record will not be changed.
  - If a stop date is reported which is later than 11-Apr-2016, the date will be set to missing and ongoing status will be set to Yes.

10.8. Process to Derive Data Cut-off for the Second Step Analysis

Database lock of the second step analysis for R668-AD-1225 study is planned for 14-Feb-2019 with data cut-off date 01-Dec-2018 for ongoing patients in Poland, Finland, Russia, New Zealand, and Singapore. All data for patients from remaining countries will be included for analysis.

The data cutoff algorithm will be applied to the raw datasets extracted from Electronic Data Capture (EDC) and IVRS system.

I. Patients to be included for the second step analysis

All screened patients will be included for analysis.

II. Data recorded during the screening period:

All data recorded during the screening period will be included for analysis.

III. Data collected through IVRS

1. All diary data collected on or before 01-Dec-2018 for ongoing patients in Poland, Finland, Russia, New Zealand, and Singapore will be kept for the second step analysis.

2. All diary data for patients from rest countries will be included for the second step analysis.

3. For the kit allocation dataset, all records will be kept for the second step analysis.

IV. Visit dependent data:

All visit dependent data on or before 01-Dec-2018 for ongoing patients in Poland, Finland, Russia, New Zealand, and Singapore will be kept for the second step analysis. All visit dependent data collected later than 01-Dec-2018 will not be included in the second step analysis datasets. Unscheduled visits with a date on or before 01-Dec-2018 will be kept on the second step analysis.

V. Visit independent/Event based data:

This includes adverse events, concomitant/prior medication and procedure:

All event records with a start date later than 01-Dec-2018 will be censored (this includes incomplete dates when the incomplete date is without any doubts later than 01-Dec-2018, e.g. the incomplete date is December 2018).

Records with a start date earlier or on 01-Dec-2018 will be kept (this includes incomplete dates when the incomplete date is earlier than 01-Dec-2018 or in case of doubts, e.g. the incomplete date for an event is November 2018, or only year 2018 or even a missing date).

For the events included in the first step analysis cut-off, several adaptions to the data will be made:

- Adverse Events:
  - If a stop date of adverse event is specified and earlier or equal to 01-Dec-2018 then the record will not be changed.
  - If a stop date of adverse event is specified and later than 01-Dec-2018, then the stop date will be deleted (set to missing) and the outcome of the adverse event (SAS variable AEOUT/AEOUTN) will be set to missing, AE ongoing status will be set to Yes.
  - If no stop date is specified and the outcome is either not yet reported (AEOUT/AEOUTN is blank) or is reported (AEOUT in (recovering/resolving, not recovered/not resolved, unknown)), then the outcome will be set to missing (AEOUT/AEOUTN is blank)
- Concomitant medication/procedure:
  - If a stop date is reported which is earlier than or on 01-Dec-2018, the record will not be changed.
  - If a stop date is reported which is later than 01-Dec-2018, the date will be set to missing and ongoing status will be set to Yes.

10.9. Algorithm to Add Not Reported Home Study Drug Injection Records Based on Drug Accountability Data for First Step analysis

Background and Rationale:

The R668-AD-1225 study is a multicenter, open-label extension study to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD who have previously participated in controlled studies of dupilumab. Study drug was dupilumab 300 mg, administered weekly via subcutaneous injections. During the study, patients were provided the option to administer the study drug outside the clinic, in which case they were dispensed drug supplies for up to 4 weeks at monthly visits and up to 8 weeks at bimonthly visits. Study drug administration and drug accountability were recorded in several sources:

The weekly study drug injections were reported in two sources.

- EDC where on-site injections were reported.
- IVRS where patients reported their weekly injections taken at home.

The dispensation and return of study drug supplies (used, partially used or unused) were reported in:

- EDC where study drug kit dispense/return data was captured

A considerable number of home-injections were not reported through IVRS system, but were actually taken by the patients. This is supported by drug accountability records, which documented the administration of study drug via the dispensation of drug supplies and the return of used kits. The purpose of this appendix to provide the algorithm for creating a more complete and accurate study drug administration record for the analysis by incorporating these data sources.

Algorithm:

1. Between the scheduled on-site dispensing visit and next on-site return visit, identify all kits dispensed including the one(s) dispensed at the unscheduled visit(s) between, and all kits returned.

2. Identify kits used between these 2 visits and count number of kits used.

   - If the question "If all vials are empty" from CRF was answered as "Yes", then it was assumed that all returned kits were taken by the patient.

   - If the question "If all vials are empty" from CRF was answered as "No", use the information from excel spreadsheet R668AD1225 Kit not empty.xls to identify which kits were not used. For each kit return record,

     I. If the column 'Adjudicated by team, if total volume was injected' was Yes, then it was assumed that all returned kits were taken by the patient.

     II. If column 'Adjudicated by team, if total volume was injected' was No, then kits identified starting from column "Kit number not used" were the returned kits not taken by the patient.

3. Identify the dose injection records reported in EDC and IVRS satisfying condition: date of dispensing visit <= date of injection < date of next on-site return visit, then count number of injections between visits.

4. If the number of injections in step #3 is less than the number of kits used in step #2, then add the not reported injections into SDTM.EX dataset. These not reported injections will be identified using variables in SUPPEX with QNAM=DATAORG and QVAL="Added by drug accountability". The Treatment variable (EXTRT) and dose variable (EXDOSE) will be populated for the newly added injections based on last observation carry forward (LOCF) method.

5. If the number of injections in step #3 is equal to or larger than the number of kits used in step #2, then no new injection record will be added into SDTM.EX dataset.

10.10. Algorithm to Derive Treatment Exposure and Duration of Observational period

The duration of treatment exposure period during the study in week is calculated as:

[(Date of last study drug injection – date of first study drug injection) + 7]/7

regardless of unplanned intermittent discontinuations. For the exposure calculation, below two treatment gaps will be excluded.

1. For patients from Germany, France, Poland and Japan who completed the 3-year treatment period under protocol amendment 6 before resuming dupilumab treatment under amendment 7, the duration from the end of treatment under amendment 6 up to the first injection date under amendment 7 will be excluded from the duration of exposure calculation.

2. For patients from Poland, Finland and France who completed the treatment period under protocol amendment 7 before resuming dupilumab treatment under amendment 8, the duration from the end of treatment under amendment 7 up to the first injection date under amendment 8 will be excluded from the duration of exposure calculation.

The following duration of exposure will be summarized using number of patients, means, SD, minimums, medians, and maximums. A summary of the number of doses will also be provided:

- The entire study treatment period
- The treatment period prior to “treatment gap”
- The treatment extension period under protocol amendment 7 for patients from Germany, France, Poland and Japan who completed 3-year treatment
- The treatment extension period under protocol amendment 8 for patients from Poland, Finland and France who completed 3-year treatment and extension period under amendment 7

The duration of observation period during the study in weeks is calculated as:

[(Date of the last visit – date of the first study medication dose) +1]/7.

For the duration of observation period calculation, below study gaps will be excluded.

1. For patients from Germany, France, Poland and Japan who completed 3-year study under protocol amendment 6, then reentered the study after reconsenting to protocol amendment 7, the duration from the end of study under amendment 6 up to date of reconsent to amendment 7 will be excluded from the duration of observation period calculation.

The following duration of observation periods will be summarized using number of patients, means, SD, minimums, medians, and maximums:

- The entire study period
- The study period prior to protocol amendment 7
- The study extension period under protocol amendment 7 for patients from Germany, France, Poland and Japan who completed 3-year treatment
- The study extension period under protocol amendment 8 for patients from Germany, Finland and France who completed 3-year treatment and extension period under amendment 7

The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest is specified as: ≥ 1 week, ≥ 4 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 24 weeks, ≥ 52 weeks, ≥ 76 weeks, ≥ 100 weeks, ≥ 104 weeks, ≥ 124 weeks, ≥ 148 weeks, ≥ 156 weeks, ≥ 164 weeks, ≥ 208 weeks, ≥ 260 weeks, ≥ 272 weeks.

As of protocol amendment 2, the weekly dose of dupilumab was changed from 200 mg to 300 mg. The number of patients exposed to 200 mg dose, the number of 200 mg doses and duration of treatment exposure with 200 mg and 300 mg in weeks will be calculated and summarized separately.

The duration of treatment exposure with 200 mg dose during the study in weeks is calculated as:

- [(Date of last 200 mg injection – date of first study drug injection) + 7]/7 for patients who did not receive 300 mg injection
- [(Date of first 300 mg injection – date of first study drug injection)]/7 for patients who received 300 mg injection

The duration of treatment exposure with 300 mg dose during the study in weeks is calculated as:

[(Date of last 300 mg injection – date of first 300 mg injection) + 7]/7

Signature Page for VV-RIM-00070032 v1.0

ESig Approval	[redacted]00
ESig Approval	[redacted]-2019 15:00:16 GMT+0000
ESig Approval	[redacted]00

Signature Page for VV-RIM-00070032 v1.0 Approved