NCT03912259

STATISTICAL ANALYSIS PLAN

Title:	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in Chinese adult patients with moderate-to-severe atopic dermatitis
Protocol:	EFC15116
Investigational product:	Dupilumab
Sponsor:	Sanofi (China) Investment Co., Ltd
Statistician:	[redacted]
Clinical Trial Manager:	[redacted]
Clinical Study Director:	[redacted]

Author:

[redacted] Date

Approvers:

Statistical Group Head Date

Clinical Development Physician Date

Table of Contents

List of abbreviations and definition of terms

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BSA	Body surface area
CRF	Case report form
CI	Confidence interval
C_{trough}	Trough concentration
DLQI	Dermatology life quality index
CPK	Creatine phosphokinase
EAIR	The exposure-adjusted incidence rate
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
EQ-5D	EuroQol five dimensions questionnaire
EQVAS	EQ visual analogue scale
ET	Early termination
ETV	Early termination visit
HLGT	High-level group term
HLT	High level term
HR	Hazard ratio
ICF	Informed consent form
ICH	International conference on harmonisation
IFN-γ	Interferon-gamma
IGA	Investigator global assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4Rα	IL-4 receptor alpha
IMP	Investigational medicinal product

IRT	Interactive response technology
ITT	Intent-to-treat
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LS	Least-squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed effect model with repeated measures
NAb	Anti-dupilumab neutralizing antibodies
NEPY	Number of events per 100 patient-years
NIMP	Noninvestigational medicinal product
NRS	Numerical rating scale
PCS	Pruritus categorical scale
PCSA	Potentially clinically significant abnormality
PD	Pharmacodynamics
PK	Pharmacokinetic
POEM	Patient oriented eczema measure
PP	Per protocol
PRO	Patient reported outcome
PT	Preferred term
q2w	Every 2 weeks
QOL	Quality of life
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMQ	Standard MedDRA Query
SOC	System organ class
SIT	Allergen-specific immunotherapy
TARC	Thymus and activation regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids

TCM	Traditional Chinese Medicine
TEAE	Treatment emergent adverse event
Th1	Type 1 helper T cell
Th2	Type 2 helper T cell
TNF	Tumor necrosis factor
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
US	United States
WBC	White blood cell
WHODD	World health organization drug dictionary
WOCF	Worst-observed-case-forward

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 EFC15116 study.

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

1.1 Background and Rationale

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

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

Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine “C” receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

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

prompted regulatory authorities to require a warning regarding the long-term safety of topical tacrolimus and pimecrolimus in their prescribing information. Repeated application of any topical therapy over a long period of time or to large surface areas also leads to reduced patient compliance. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Oral immunosuppressants and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Diabetes, hypertension, and osteoporosis are side effects associated with systemic corticosteroids and there is also the risk of rebound after steroid discontinuation.

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

Up-regulation of IL-4 and IL-13 have been implicated as an important inflammatory component of AD disease progression. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL 13 receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction.

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. This population includes patients who are often treated with systemic corticosteroids, as well as other non-selective immunosuppressants, including cyclosporine, which are associated with significant toxicities. Dupilumab is being developed as a potential alternative to oral corticosteroids, calcineurin inhibitors, and other systemic immonosuppressive drugs, which are used for treatment of AD patients and have numerous, considerable adverse drug reactions (ADRs), and may increase the risk of serious infection. A more focused immunomodulatory agent such as dupilumab may have more limited effects on the immune system and potentially fewer ADRs.

Data with dupilumab have, to date, demonstrated efficacy, safety, and tolerability in a patient population with moderate-to-severe AD. In global phase 2 and phase 3 studies, treatment with dupilumab monotherapy consistently and significantly cleared or reduced the extent and severity of AD lesions and relieved pruritus, with superior treatment effect to placebo demonstrated by an array of clinically relevant endpoints.

The dupilumab safety database consists of over 3000 patients exposed to dupilumab across all indications, including over 2500 in AD. Dupilumab was well tolerated and generally safe when used in patients with moderate-to-severe AD.

This is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety in Chinese adult patients with moderate-to-severe AD whose disease cannot be adequately

controlled with topical medications or for whom topical treatment is medically inadvisable. This study will generate information in Chinese AD patients regarding monotherapy with dupilumab compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. The dose regimen of subcutaneous (SC) dupilumab selected for this study is 300 mg every 2 weeks (q2w). The dose of dupilumab in this study were based on the efficacy and safety results from global pivotal Phase 3 studies (R668-AD-1334 and R668-AD-1416).

1.2 Study Objectives

1.2.1 Primary Objective

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

1.2.2 Secondary Objectives

- To evaluate the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD.
- To evaluate the effect of dupilumab on improving patient reported outcomes (PROs)
- To evaluate dupilumab immunogenicity

1.2.3 Other Objectives

- To evaluate dupilumab systemic exposure

[redacted]

1.3 Modifications from the Statistical Section in the Final Protocol

Modifications from the Amended protocol 1 (final protocol)

1. concomitant medication/procedure

Any concomitant treatment is considered from the first dose of study drug in the SAP instead of the time of informed consent in the protocol.

2. Potentially clinically significant abnormality (PCSA)

PCSA is applied to clinical laboratory evaluations and vital signs in SAP, while PCSA was applied to ECG as well in the protocol.

1.4 Modification from the Previously Approved SAP

NA

2 INVESTIGATIONAL PLAN

2.1 Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, parallel-group phase 3 study to evaluate the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study period included 16-week treatment period 12-week follow-up. Eligible patients will be randomized in a 1:1 ratio to receive q2w SC injections of 300 mg dupilumab, or matching placebo. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) 3] versus severe [IGA 4] AD).

2.2 Sample Size and Power Considerations

A total of 160 patients (with a randomization ratio of 1:1, 80 patients in each of the dupilumab 300 mg q2w and the placebo groups) will be enrolled in this study.

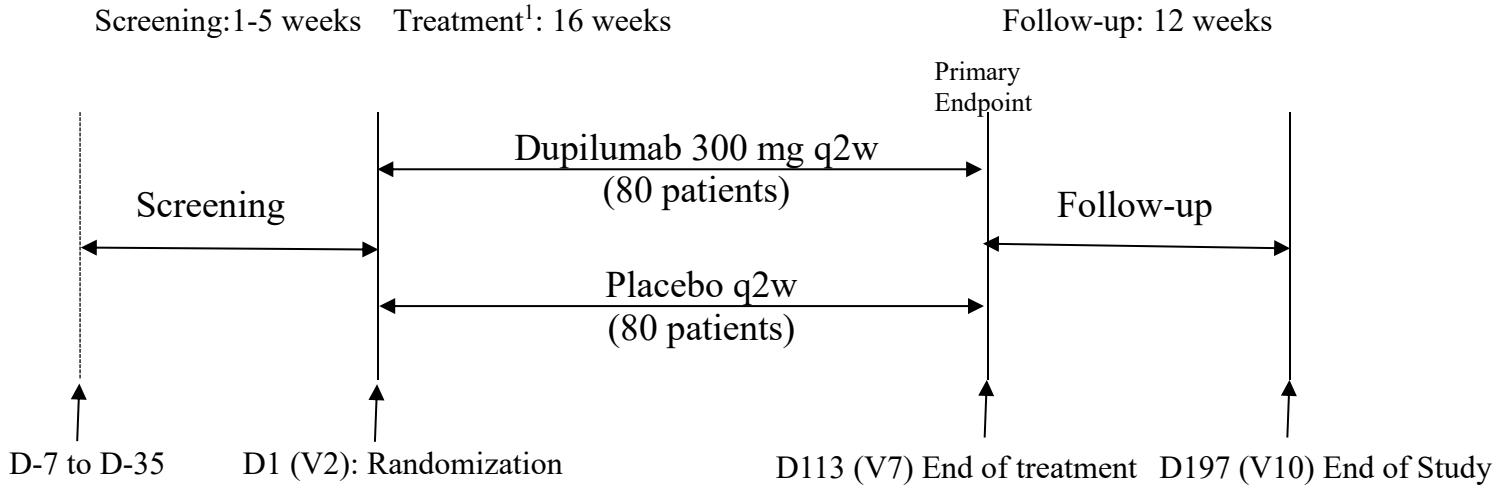
The study will have 94% power to detect the difference between dupilumab and the placebo. It is based on the following assumptions:

- The percentages of patients who achieve an IGA score of 0 to 1 and a reduction from baseline ≥2 points at Week 16 are 37% and 12% for dupilumab and placebo, respectively.
- A two-sided continuity corrected Chi-square test with the significance level of 0.05.

Calculations were made using nQuery Advisor 7.0 Software.

2.3 Study Plan

The study consists of a screening period, a treatment period and a follow-up period as presented below:



1 Patients will receive a loading dose of the IMP on Day 1 and then receive the IMP every two weeks during the subsequent 14 weeks.
IMP = investigational medicinal product, q2w = once every 2 weeks.

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening for 7-35 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements.

Patients may be rescreened once if they fail the screening evaluation for reasons related to incidental transitory conditions. Patients will be required to apply moisturizers (emollients) at least twice daily for at least 7 days before randomization and continue throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of nonlesional skin designated for such assessments for at least 8 hours before each clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo Day 1/baseline assessments and will be randomized to receive q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on Day 1, or matching placebo (including doubling the amount of placebo on Day 1 to match the loading dose). Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Following the initial dose of 600 mg, the investigational medicinal product (IMP) will be administered 300 mg at Weeks 2, 4, 6, 8, 10, 12, and 14. Patients will remain at the study site for a minimum of 30 minutes after each injection at the study site. Patients will have the option to self-administer the IMP (or have a caregiver administer the IMP) outside the study site during weeks in which no clinic visit is scheduled (ie, Weeks 6, 10, and 14). Patients (and/or caregivers) will be trained on injecting the IMP at Visit 2 (Day 1) through Visit 4 (Week 4), or until competency has been demonstrated. Patients who do not want to self-inject may have the clinic staff administer all the IMP injections in the clinic.

During the 16-week treatment period, patients will have study visits at Weeks 0, 2, 4, 8, 12, and 16. Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Appendix 10.2).

The end of treatment visit will occur at Week 16, 2 week after the last dose of study drug. The primary endpoint will be determined at Week 16.

Follow-up visits will occur every 4 weeks from Week 20 through Week 28. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach below the lower limit of quantification in most patients after the last dose of dupilumab. The end of study visit will occur at Week 28.

3 ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations of analysis will be used for all statistical analyses.

3.1 Intent-to-treat Population

The intent-to-treat (ITT) population includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the interactive response technology (IRT) at randomization (as randomized). This is the primary analysis population for efficacy analyses.

For any patient who was randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

Patients who temporarily or permanently discontinue from the IMP and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits and complete all study assessments per the study schedule.

3.2 Per Protocol Population

The per protocol (PP) population includes all patients in the ITT population except for those who are excluded because of major efficacy-related protocol violations.

A major efficacy-related protocol violation is one that may affect the interpretation of study efficacy results. The criteria of major efficacy-related protocol deviation are defined as following:

- Patients who did not receive treatment as randomized, which are defined as
  - patients on placebo but accidentally exposed to dupilumab,
  - patients on dupilumab receiving placebo whose compliance with the dupilumab injection is <80% by counting placebo injections as missing
- Any major violations of efficacy-related entry criteria (Appendix 10.7)
  - Inclusion criteria 3, 4, 5 and 6
  - Exclusion criteria 3 ,4, 5, 6, 7, 8 and 9
- The percentage of a patient's compliance with the IMP injection is <80% or >120% of the scheduled doses during the study treatment period
- Patients who were randomized more than once
- Patients who were randomized but not treated

Final determination of the PP population will be made in the blinded manner prior to the database lock.

3.3 Safety Population

The safety population consists all randomized patients who receive any IMP. Patients will be analyzed according to the treatment they actually received (as treated).

The actual treatment group is defined by the following rules:

- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be dupilumab
- For patients on dupilumab but accidentally received placebo, the actual treatment group allocation for as-treated analysis will be the treatment as randomized if at least one dose or part of a dose of dupilumab was received
- For patients on dupilumab but accidentally received placebo, the actual treatment group allocation for as-treated analysis will be placebo if the patient did not exposed to any dupilumab

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized

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

The pre-treatment period is defined as the time from signing the informed consent form (ICF) to before the first dose of IMP. The treatment emergent period is defined as the time from first dose of IMP (Day 1) to the end of the study.

For safety summarizes, three analysis period are defined as follows:

- On-treatment period is defined as day 1 to the day of last dose of IMP + 14 days or early termination date from study, whichever comes first
- Follow-up period is defined as the last dose of IMP + 15 days to the date of the end of study
- Overall study period is defined as day 1 to the date of the end of study, consisting of both the treatment and follow-up periods

The safety population will be the basis for the analyses for the week 16 treatment period and overall study period; however, for the analyses for the follow-up period, only a subset of safety population will be included, which is defined as the patients who entered the follow-up and had at least one visit after week 16 treatment visit.

3.4 Pharmacokinetic (PK) Population

The PK population consists of all patients in the safety population with at least one evaluable functional dupilumab concentration result following the first dose of study drug up to Week 16. Functional dupilumab concentration will also be reported in those patients who completed the study through week 28. Patients will be analyzed according to the treatment actually received.

3.5 Anti-Drug Antibody (ADA) Population

The ADA population includes all patients in the safety population with at least one reportable ADA result (either “ADA negative” or “ADA positive”) after first dose of the IMP. Patients will be analyzed according to the treatment actually received.

4 ANALYSIS VARIABLES

4.1 Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age at screening with grouping (year; ≥18-<40, ≥40-<65, ≥65), Sex, Race (Asian), Baseline weight with grouping (kilograms [kg], <70; ≥70-<100, ≥100), Baseline Height (centimeters [cm]), and Baseline BMI (kg/m^2; <15, ≥15-<25, ≥25-<30, ≥30; <18.5, ≥18.5-<24, ≥24-<28, ≥28), Patients with inadequate response to topicals (Yes/No), Topical treatments are medically inadvisable for the patient (Yes/No)
- Baseline disease characteristics: Duration of AD disease with grouping (years; <26 and ≥26), Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, Pruritus numerical rating scale (NRS) for maximum or average itch intensity, Pruritus categorical scale (PCS), Body Surface Area (BSA) Involvement of Atopic Dermatitis, Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and EuroQol five dimensions questionnaire (EQ-5D)

4.2 Medical History and Atopic Disease Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Family history of atopic/allergic conditions will be collected, including atopic dermatitis, asthma, allergic conjunctivitis (keratoconjunctivitis), allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy, hives and other allergies (medications, animals, plants, mold, dust mites, etc.).

4.3 Pre-treatment/ Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the final study visit (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). Patients will be counted once in all ATC categories linked to the medication. Procedures will be coded to a PT and associated primary SOC using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the first IMP. Pre-treatment medications/procedures can be discontinued before first administration or can be ongoing during treatment period.

Concomitant medications/procedures: medications taken or procedures performed following the first IMP through the EOS visit.

Background treatment: All patients are required to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization and to continue throughout the study.

Prohibited concomitant medications/procedures during the study

The following treatments are prohibited during the study:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/immunomodulating drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, and Janus kinase inhibitors)
- Initiation or uptitration of allergen-specific immunotherapy (SIT). Patients on SIT prior to the screening visit must be on a stable dose and remain on that dose during the study
- Any other medications for AD that could have interfered with efficacy outcomes or affected the evaluation for AD severity. Examples of such medications include coal tar products, other staining topical products, traditional Chinese medicine (TCM), or any other therapeutic agents for AD that were not properly evaluated in clinical trials

The IMP will be discontinued if the following is used through Week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/immunomodulating drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, and Janus kinase inhibitors)

The following concomitant procedures are prohibited during study participation:

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

Rescue treatments for AD: If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD with otherwise prohibited medication or procedure may be provided to study patients at the discretion of the investigator.

Patients who receive rescue treatment during the study treatment period will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only. If possible, Investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment.

If a patient receives rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/immunomodulating drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, Janus kinase inhibitors, biologic agents, etc), the IMP will be immediately discontinued.

After the treatment with these medications is completed, the IMP may be resumed if deemed appropriate by the Investigator and the sponsor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

All patients will complete the schedule of study visits and assessments whether or not they complete the treatment with the IMP and whether or not they receive rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure. The rescue treatments will be adjudicated by the clinical study director and the adjudication procedure will be documented.

4.4 Efficacy Variables

4.4.1 Primary Efficacy Variable

The primary endpoint is:

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

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument used in clinical studies to rate the severity of AD globally. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of the skin lesions based on erythema and papulation/infiltration. The IGA score will be assessed at every scheduled and unscheduled clinic visit.

4.4.2 Secondary Efficacy Variables

The secondary endpoints are:

- Proportion of patients with EASI-75 response (reduction of EASI score ≥75% from baseline) at Week 16
- Proportion of patients with reduction of weekly average of peak daily pruritus NRS ≥4 from baseline to Week 16
- Proportion of patients with reduction of weekly average of peak daily pruritus NRS ≥3 from baseline to Week 16
- Percent change from baseline to Week 16 in weekly average of peak daily Pruritus NRS
- Change from baseline to Week 16 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to Week 16
- Change from baseline to Week 16 in percent BSA of AD involvement
- Change from baseline to Week 16 in DLQI
- Change from baseline to Week 16 in POEM
- Percent change from baseline to Week 2 in weekly average of peak daily Pruritus NRS
- Absolute and percent change from baseline to Week 16 in EQ-5D
- Proportion of patients who achieve reduction of IGA score by ≥2 from baseline to Week 16
- The proportion of patients with EASI-50 (≥50% improvement from baseline) at Week 16
- The proportion of patients with EASI-90 (≥90% improvement from baseline) at Week 16

- Proportion of patients achieving IGA 0 to 1 and a reduction of ≥2 points from baseline through Week 16
- Absolute and percent changes in EASI score from baseline through Week 16
- Absolute and percent changes in weekly average of peak daily pruritus NRS score from baseline through Week 16
- The proportion of patients who responded "absence of pruritus" or "mild pruritus" in the pruritus categorical scale at Week 16
- Number of days and proportion of patients with sick leave/missed school days

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). Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity by the Investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

For each body region (head, trunk, upper limbs, and lower limbs), EASI score = (sum of the four AD disease characteristics scores) multiply (area of AD involvement score). The total EASI sore is the weighted total of the body region EASI scores using the weights 10% = head, 20% = upper limbs, 30% = trunk, 40% = lower limbs. 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 AD.

The EASI will be collected at every scheduled and unscheduled clinic visit.

Pruritus Numeric Rating Scale (NRS)

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

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

Patients will be instructed on using the pruritus reporting system to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale daily. Clinical sites will receive alerts when patients do not complete the pruritus reporting system items. Sites will be expected to contact patients who have missed 2 consecutive entries to encourage patient compliance. The Investigator will check patients' reports at each visit.

If there are multiple NRS to the same question (average or maximum itch intensity) collected on the same day, average of all the scores collected will be taken.

The baseline NRS is defined as the prorated average of the NRSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline NRS, The mean weekly NRS is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3. The baseline NRS and mean weekly NRS will be calculated for average itch intensity and peak itch intensity separately.

Body Surface Area (BSA) Involvement of Atopic Dermatitis

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

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire (Badia 1999) used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on Quality of Life (QOL). The format is a simple response to (0 to 3, where 0 = not at all; 1 = a little, 2 = a lot, 3 = very much) 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. For question 7, 0 = not relevant, 1= no + a little, 2 = no + a lot, 3 = yes. For general inflammatory skin conditions a change in DLQI score of at least 4 points is considered clinically important (Basra et al, 2015).The DLQI will be assessed at every scheduled and unscheduled clinic visit.

Handling missing items from DLQI:

i. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
ii. If two or more questions are left unanswered the questionnaire is not scored.
iii. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
iv. If question 7 is answered “no” or “not relevant”, but either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
v. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

Patient Oriented Eczema Measure (POEM)

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

If two or more response options are selected for a question, then the response option with the highest score is recorded. If one question of the seven is left unanswered, then that question is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28. If two or more questions are left unanswered, then the questionnaire is not scored and is set to missing.

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

EuroQol five dimensions questionnaire (EQ-5D)

The EuroQoL 5-Dimension Health Questionnaire 3 Level (EQ-5D-3L) is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-3L is a self-administered questionnaire used to assess health status 'today' which consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS).

The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement (ie, no problems, some problems, or severe problems) in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state, potentially producing 243 different states. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health." Values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model and weighted according to the social preferences of the Chinese population. The minimum value for the single index utility score is 0.1702. Appendix 10.4 provides the SAS code to derive the index utility score using Chinese based population (Zhu, 2018).

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

EQ-5D-3L will be assessed at the following visits: baseline (Day 1), Week 8, Week 16 (EOT), Week 28 (EOS), and early termination (ET) visit.

Pruritus Categorical Scale (PCS)

The PCS is a 4-point scale used to assess symptoms that has been used in clinical studies of AD and there is less of a tendency for patients to provide an "average" response than there might be with a 5-point scale (Kaufmann 2006). The scale is rated as follows: 0: absence of pruritus; 1: mild pruritus (occasional slight itching/scratching); 2: moderate pruritus (constant or intermittent itching/scratching that does not disturb sleep) and 3: severe pruritus (bothersome itching/scratching that disturbs sleep).

Patients will be instructed on using the pruritus reporting system to complete the PCS at the screening visit. Patients will complete the categorical scale daily. Clinical sites will receive alerts when patients do not complete the pruritus reporting system items. Sites will be expected to contact patients who have missed 2 consecutive entries to encourage patient compliance. The Investigator will check patients' reports at each visit.

For each day, if there are multiple PCS scores collected on the same day, the maximum (worst) of all the scores collected will be chosen. For each week, calculate round prorated average of

collected scores for Category Score. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3 round to 1.0.

The baseline PCS is defined as the round prorated average of the PCSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1).

Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at the following visits: baseline (Day 1), Week 4, Week 8, Week 12, Week 16 (EOT), Week 20, Week 24, Week 28 (EOS), ET and unscheduled visits.

4.5 Safety Variables

4.5.1 Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "PT", "High Level Term (HLT)", "High-level Group Term (HLGT)" and the associated primary "SOC" using the version of MedDRA currently in effect at Sanofi at the time of database lock.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is a medically important event.

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion, and/or
- Defined as an AESI

Pretreatment AEs are defined as AEs that developed or worsened during the pre-treatment period. Treatment emergent adverse events (TEAEs) are defined as AEs that developed or worsened during the treatment-emergent period.

4.5.2 Laboratory Safety Variables

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

Blood samples for serum chemistry and hematology testing will be collected at screening (day -7 to day -35), baseline (Day 1), Week 8, Week 16 (EOT), Week 28 (EOS), ET and unscheduled visits. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory.

Blood Chemistry

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

Note: Direct and indirect bilirubin will be measured when the total bilirubin is above the upper limit of normal (ULN); CPK isoenzymes will be reflexly measured when CPK >5 ULN

Hematology with Differential

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

Urinalysis

Urine samples for urinalysis will be collected to measure overall patient health at screening (day -7 to day -35), baseline (Day 1), Week 16, Week 28 (EOS), ET and unscheduled visits.

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

Note: Microscopic analysis will only be done in the vent of abnormal dipstick results

Pregnancy testing (serum or urine) will be performed for all women of childbearing potential at screening (day -7 to day -35), baseline (Day 1), Week 4, Week 8, Week 12, Week 16 (EOT), Week 28 (EOS), ET and unscheduled visits.

4.5.3 Vital Sign Variables

The following vital signs parameters will be collected:

- Weight (kg) and height (cm)
- Respiratory rate (breaths/min)
- Heart rate (beats/min)
- Systolic and diastolic blood pressures (mmHg)
- Body temperature (^{o}C)

Weight is determined at screening and baseline (Day 1), and Week 16 (EOT), Week 28 (EOS), ET and unscheduled visits. Height is only measure at screening. Other vital signs are collected pre-dose at every scheduled and unscheduled clinic visit.

4.5.4 12-Lead Electrocardiography (ECG) Variable

The ECG interpretation variable are dichotomized to normal and abnormal. Electrocardiograms will be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at screening, Week 16 (EOT), and Week 28 (EOS) or ET visits.

4.5.5 Physical Examination Variable

The physical examination variable values are dichotomized to normal and abnormal.

A thorough and complete physical examination will be performed at screening, Week 16 (EOT), and Week 28 (EOS) or ET visits. If patients have any symptom or sign of ocular surface diseases, eg, conjunctivitis and blepharitis, at screening or during study period, ophthalmological examinations should be done.

4.5.6 Immunogenicity Variables

The immunogenicity variables are ADA status, ADA titer and anti-dupilumab neutralizing antibodies (NAb) status.

Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA population.

ADA response categories are defined as follows:

- Negative in ADA assay at all time points analyzed
- Preexisting immunoreactivity
  Defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels
- Treatment emergent response in the ADA assay
  Defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment emergent responses may be further characterized as Persistent, Indeterminate or Transient

  - Persistent Response - treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period [greater than 85 days], with no ADA negative samples or any missing sample in between
  - Indeterminate Response - treatment-emergent response with only the last collected sample positive in the ADA assay
  - Transient Response - treatment emergent ADA positive response that is not considered persistent or indeterminate
- Treatment boosted response in the ADA assay
  Defined as a positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive

ADA status are defined as follows:

- ADA positive patients, that is patients with treatment-emergent or treatment boosted response.
- ADA negative patients, that is patients with preexisting immunoreactivity or negative in the ADA assay at all time points.

Titer Category (Maximum titer values):

- Low (titer <1000)
- Moderate (1000 ⩽ titer ⩽ 10 000)
- High (titer >10 000)

Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.2. ADA analysis will be conducted on sample collected at baseline, Week 16 (EOT), Week 28 (EOS), and ET. All samples that are positive in the ADA assay will be further characterized for ADA titers and for the presence of NAb. Samples that tested negative for ADA are considered to be NAb negative and are therefore not analyzed in the NAb assay. The NAb status is categorized as follows:

- Negative (samples negative in the ADA assay, and samples positive in ADA assay that are negative in the NAb assay)
- Positive (samples positive in both the ADA and NAb assays)

4.6 Pharmacokinetic (PK) Variables

Pharmacokinetic variables include trough concentration (C_{trough}) over time until week 16. Samples for measurement of functional dupilumab concentration in serum will be collected before the injection of the IMP at baseline (Day 1), Week 12, Week 16 (EOT), Week 28 (EOS), ET and unscheduled visits.

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

5 STATISTICAL METHODS

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

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

5.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group based on ITT population.

5.2 Medical History and Atopic Disease Medical History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by internationally agreed order of SOC followed by PT sorted in alphabetical order based on the overall incidence across treatment groups.

Number and percentage of patients with personal history (current/past) of atopic/allergic conditions will be summarized for each treatment groups. Appendix 10.6 provides a list of personal history of atopic/allergic conditions search criteria. Blinded manual adjudication will be required by the study medical monitor, before database locks.

Number and percentage of patients with family history of atopic/allergic conditions will be summarized by the categories listed on the case report form (CRF) for each treatment groups.

5.3 Pre-treatment/Concomitant Medications/Procedures

Number and proportion of patients taking pre-treatment/concomitant medications and rescue medications will be summarized, sorted by decreasing frequency of ATC Level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), based on the overall incidence across treatment groups.

Procedures will be summarized by treatment group by primary SOC (sorted by internationally agreed order) and PT (sorted in alphabetical order), sorting are based on the overall incidence across treatment groups.

The detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized by topical and systemic groups. Kaplan Meier curves for time to first rescue use will be generated. Listing of rescue use will be presented.

The compliance of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group.

5.4 Patient Disposition

The following summaries by table will be provided:

- The total number of screened patients: patients who signed the informed consent
- The total number of randomized patients: patients with a treatment kit number allocated and recorded in the IRT database, and regardless of whether the treatment kit was used or not
- The total number of patients in each analysis population

- The total number of patients who discontinued the study treatment and the reasons for the discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation

The following listings will be provided:

- Listing of patient disposition including: date of randomization, last visit, dosing, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- Summary table with listing of protocol deviations will be provided

5.5 Dose administration

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. The compliance with protocol-defined study treatment will be calculated as follows:

Treatment compliance= (number of IMP injections during exposure period)/(number of planned IMP injections during exposure period) x 100%

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

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be summarized descriptively and will be presented by the following specific ranges for each treatment group: <80%, 80% - 120%, and >120%.

5.6 Treatment Exposure and Observation Period

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

(Date of last IMP injection – date of first IMP injection) + 14 days regardless of unplanned intermittent discontinuations.

The duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well:

≥ 14 days, ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥ 70 days, ≥ 84 days, ≥98 days, ≥112 days.

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

(Date of the last study visit – date of the first IMP injection) +1.

The duration of observation period will be summarized descriptively as a quantitative data (n, mean, SD, median, minimum and maximum). In addition, the number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest is specified as:

≥ 15 days, ≥ 29 days, ≥ 43 days, ≥ 57 days, ≥ 71 days, ≥ 85 days, ≥ 99 days, ≥113 days, ≥141 days, ≥169 days, ≥197 days.

5.7 Analyses of Efficacy Variables

For all efficacy variables, the analysis will be comparisons of dupilumab and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested:

H0: No treatment difference between dupilumab and placebo ($p_{dupilumab} = p_{placebo}$, where p stands for the proportion of responders in a treatment group)

H1: There is a treatment difference between dupilumab and placebo ($p_{dupilumab} \neq p_{placebo}$)

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

Subgroups are defined by key baseline factors recorded on the CRF and listed to be considered for primary and secondary (EASI and/or Pruritus NRS) efficacy analyses:

- Age group (≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Duration of AD (< 26 years, ≥26 years)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)
- BMI (<15, ≥15-<25, ≥25-<30, ≥30)
- Baseline disease severity [moderate (IGA=3) and severe (IGA=4)]
- Baseline moderated-to-severe EASI (<20, ≥20)
- Baseline severe EASI (<25, ≥25)
- Baseline peak pruritus NRS (<7, ≥7)
- Baseline Body Surface Area (BSA) (≥10%-<30%, ≥30%-<50%, ≥50%)
- Previous use of systemic immunosuppressants (Yes, No)
- Previous use of systemic cyclosporine (Yes, No), and/or Azathioprine (Aza) (Yes, No), and/or Methotrexate (MTX) (Yes, No)
- History of asthma (Yes, No)
- History of nasal polys (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergies (Yes, No)

5.7.1 Analysis of Primary Efficacy Variables

The Cochran-Mantel-Haenszel test adjusted by baseline disease severity (moderate or severe) will be used for the percentage of patients with both IGA 0 or 1 and a reduction from baseline of ≥2 points at Week 16.

Handling of dropouts or adjudicated rescue therapy or missing value for the binary response variables as the primary analysis:

- If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal.
- If rescue medication or procedure is used (see Section 4.3 for rescue), the patient will be specified as a non-responder from the time the rescue is used.
- Patients with missing values at Week 16 will be counted as non-responders at Week 16.

Sensitivity analyses

1. Post-baseline last observation carried forward (LOCF) approach after censoring for rescue medication or procedure use or study withdrawal to determine patient's status at Week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. For patients with only baseline value, the baseline value will be carried forward to Week 16.
2. All observed data regardless of rescue medication or procedure use or data is collected after study withdrawal, will be included for the primary endpoint. Patients with missing values will be counted as non-responders.
3. Post-baseline worst-observed-case-forward (WOCF) approach after censoring for rescue medication or procedure use to determine patient's status at Week 16. For patients with only baseline value, the baseline value will be carried forward to Week 16. For the remaining missing values at Week 16 after imputation, multiple imputation (MI) approach following the oval pattern will be used to do the imputation.

The primary efficacy analyses will be performed on the ITT population, as well as on the PP population as a supporting analysis.

5.7.2 Analyses of Secondary Efficacy Variables

The binary secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoints.

The continuous endpoints will be analyzed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model as the primary analysis. Patients' efficacy data after rescue medication or procedure up to Week 16 or after study withdrawal up to Week 16 will be set to missing and then imputed by the MI method. Missing data from the ITT population will be imputed 50 times to generate 50 complete data sets by using the SAS MI procedure (using Markov Chain Monte Carlo method) following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment group, randomization strata (disease severity), and relevant baseline value.

The Week 16 data of each of the 50 complete datasets will be analyzed using an ANCOVA model with treatment, randomization strata (disease severity), and relevant baseline value included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula.

The imputation model will include:

- The variables in the ANCOVA model, including treatment group, randomization strata and relevant baseline value
- Measured continuous endpoint values in each scheduled visit up to Week 16

Categorical variables included in above model (ie, treatment group and randomization strata) are not expected to be missing.

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

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

Sensitivity analyses

In addition to the MI method described previously, sensitivity analyses for the continuous endpoints for EASI and/or Pruritus NRS will be conducted as described below:

1. This sensitivity analysis will use a mixed-effect model repeated measures (MMRM). The model will include factors (fixed effects) for treatment, randomization strata, visit, treatment-by-visit interaction, and relevant baseline values. An unstructured covariance matrix will be used to model the within-patient errors. Denominator degrees of freedom will be estimated using approximation of SATTERTH. The efficacy data will be set to missing after rescue medication or procedure is used or after study withdrawal. Afterwards no imputation will be made.

   The MMRM model will provide baseline adjusted least-squares (LS) means at Week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p values for treatment comparisons. The graph of LS-mean +/- SE by visit will be provided.

2. The sensitivity analysis based on all observed data regardless if rescue treatment is used or if data are collected after withdrawal using MI method will be performed.

3. This sensitivity analysis will use ANCOVA model, including the treatment group, randomization strata and relevant baseline value. The efficacy data will be set to missing after rescue medication or procedure is used or after study withdrawal. The post-baseline LOCF method will then be used to impute missing values.

4. This sensitivity analysis will use ANCOVA model, including the treatment group, randomization strata and relevant baseline value. The efficacy data will be set to missing after rescue medication or procedure is used or after study withdrawal. The post-baseline WOCF method will then be used to impute missing values.

Multiplicity Considerations

If the primary endpoint is significant at the 0.05 level, the secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.05 significance level of the prior one.

The hierarchy for the secondary endpoints is as follows:

- Proportion of patients with EASI-75 response (reduction of EASI score ≥75% from baseline) at Week 16

- Proportion of patients with reduction of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 16
- Proportion of patients with reduction of weekly average of peak daily Pruritus NRS ≥3 from baseline to Week 16
- Percent change from baseline to Week 16 in weekly average of peak daily Pruritus NRS
- Change from baseline to Week 16 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to Week 16
- The proportion of patients with EASI-50 (≥50% improvement from baseline) at Week 16
- The proportion of patients with EASI-90 (≥90% improvement from baseline) at Week 16
- Change from baseline to Week 16 in percent BSA of AD involvement
- Change from baseline to Week 16 in DLQI
- Change from baseline to Week 16 in POEM
- Percent change from baseline to Week 2 in weekly average of peak daily Pruritus NRS

5.8 Analysis of Safety Data

The summary of safety and tolerance will be performed based on the safety population.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, vital signs, physical examination, 12-lead ECG, and immunogenicity.

The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds (Appendix 10.3) based on literature review and defined by the sponsor for clinical laboratory tests, and vital signs.

Treatment-emergent PCSA is any PCSA developed or worsened in severity compared to the baseline during the treatment-emergent period. The time interval to detect any event or abnormality is between the first injection of study drug and EOS. All evaluations performed during the time interval will be taking into account when determine which patients had at least one PCSA, including unscheduled or repeated evaluations.

5.8.1 Analysis of Adverse Events

The number and proportion of patients will be summarized separately for the week 16 treatment period, the follow-up period and overall study period, described in Section 3.3. The incidence tables will present by primary SOC (sorted by internationally agreed order for the dupilumab group), HLGT, HLT and PT sorted in alphabetical order for each treatment group and selected subgroup, including the number (n) and percentage (%) of patients experiencing a TEAE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

TEAEs will also be summarized by severity and relationship to IMP for each treatment group, presented by primary SOC and PT.

The time to first TEAE of special interest (AESIs) during the week 16 treatment period will be assessed by Kaplan-Meier estimates (K-M plot). The time is defined as the date of first event – the date of first dose + 1. Patients without an event will be censored at the end of 16-week treatment period. Graphs of cumulative incidence rate over time will be presented by treatment group.

Listings will be provided for all TEAEs, SAEs, death and TEAEs leading to permanent treatment discontinuation by treatment group and patient. Flags will be used to indicate on-treatment death.

The following variables will be included in the listing:

- Patient ID
- Treatment group
- Age/sex/race
- SOC
- HLGT
- HLT
- PT
- Verbatim Term
- AE start date and end date/ongoing
- AE Duration
- Relationship of AE to study drug: unrelated or related
- Action taken: drug interrupted, dose reduced, drug withdrawn, drug not changed, dose increased, or not applicable
- Severity: using a 3–point scale (mild, moderate, or severe)
- Outcome: recovered or resolved, recovered or resolved with sequelae, recovering or resolving, not recovered or not resolved, fatal or unknown

Overall TEAE summary

The overall summary of TEAEs will be provided with number and proportions of patients with any:

- TEAE
- TEAE related to study drug
- TEAE by severity
- Serious TEAE
- TEAE of special interest (AESI)
- TEAE leading to death
- TEAE leading to permanent treatment discontinuation

AESI:

- Anaphylactic reactions
- Systemic or extensive hypersensitivity reactions
- Malignancy
- Helminthic infections
- Suicide-related events
- Blepharitis (severe or serious or lasting ≥4 weeks)
- Any type of conjunctivitis (severe or serious or lasting ≥4 weeks)
- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP
- Symptomatic overdose (serious or nonserious) with IMP/NIMP

Appendix 10.5 provides a list of AESIs search criteria.

TEAE Incidence

Number and proportions of patients reporting TEAEs will be summarized for the following TEAEs:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLGT/HLT/PT
  - TEAEs by SOC/PT with PT ≥5% in any treatment groups
  - TEAEs by severity by SOC/PT
  - TEAEs by relationship to IMP assessed by the investigator by SOC/PT
  - TEAE of special interest by category and PT
- Serious TEAEs
  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLGT/HLT/PT
  - Serious TEAEs related to study drug as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/HLGT/HLT/PT
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the investigator) by SOC/HLGT/HLT/PT

Death

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received
- Death in nonrandomized patients or randomized and not treat patients

5.8.2 Analysis of Clinical Laboratory Measurements

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

- Descriptive statistics of baseline laboratory test results and change from baseline to each visit
- Number and percentage of patients with a treatment-emergent PCSA
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

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

5.8.3 Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of baseline vital sign variable and change from baseline to each visit
- Number and percentage of patients with a treatment-emergent PCSA
- 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 PCSA, depending on data.

5.8.4 Analysis of Physical Examination

Number and percentage of patients with abnormal physical examination will be summarized at baseline, end of treatment period and end of study by treatment group. A summary of treatment-emergent abnormal findings will be provided.

5.8.5 Analysis of 12-Lead ECG

Number and percentage of patients with abnormal ECG interpretation will be summarized at baseline, end of treatment period and end of study by treatment group.

5.8.6 Analysis of Immunogenicity Data

5.8.6.1 Analysis of ADA Data

The incidence of ADA response variables will be summarized using descriptive statistics in the ADA population. The NAb relevant analyses will be based on all patients in the ADA population with at least one non-missing NAb result (either "NAb negative" or "NAb positive") after first dose of the IMP.

Frequency tables of the proportion of patients developing ADA positivity in the ADA assay, Neutralizing antibody status in the NAb assay, pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent, indeterminate and transient ADA responses and titers will be presented as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Percentages are rounded to 3 significant figures; therefore, there may be slight differences between subgroups and overall percentages.

Listings of anti-dupilumab antibody status, neutralizing status, and titers per time point and treatment group will be provided.

The following summaries will be performed on the ADA population:

- Number (%) of patients ADA negative at all time points analyzed by treatment group
- ADA titers using descriptive statistics (mean, standard deviation, geometric mean, median, minimum and maximum) by treatment group
- Number (%) of patients with neutralizing antibody status (negative or positive) by treatment group
- Number (%) of patients with pre-existing ADA, treatment-emergent ADA, and treatment boosted response ADA response by treatment group
- Number (%) of patients with persistent, transient and indeterminate treatment-emergent ADA response by treatment group

5.8.6.2 Immunogenicity and Pharmacokinetics

Potential associations between immunogenicity and serum concentration of dupilumab will be explored for dupilumab dose group. Plot of serum concentration of functional dupilumab may be provided for analyzing the potential impact of ADA/NAb status, ADA titer on PK.

5.8.6.3 Immunogenicity and Safety and Efficacy

Association of ADA responses and safety events may be performed in the ADA population.

The safety assessment will focus on the following events:

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

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

In addition, the primary endpoint and key secondary efficacy endpoints will be summarized in patients with and without ADA (positive vs. negative) and neutralizing antibody (positive or negative) status if applicable.

5.9 Analysis of Pharmacokinetic Data

5.9.1 Descriptive Analysis of Dupilumab Concentrations in Serum

Serum concentrations of dupilumab will be summarized in the PK population using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV, %), median, minimum, first quartile, third quartile and maximum per sampling time by treatment group. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. Percentages are rounded to 3 significant figures; therefore, slight differences between subgroups and overall percentages may occur.

Concentrations of functional dupilumab below the lower limit of quantification (LLOQ) are set to zero. Line plots of mean (SD) and median functional dupilumab concentrations will be presented over nominal time (weeks; linear and log scales). Individual line plots of functional dupilumab concentration (spaghetti plots) will be presented over actual time (weeks) on linear and log scales. Individual scatter plots will be presented over nominal time (weeks). When the scale is linear, concentrations below the LLOQ are set to zero. In the log-scaled figures, concentrations below the LLOQ are imputed as LLOQ/2.

Dupilumab trough concentration on week 16 will be summarized based on baseline body weight categories (<70 kg, ≥70-<100 kg, ≥100 kg).

5.9.2 Analysis of Concentration-Response Relationship

The concentration-response (C-R) relationship will be analyzed by comparing the time course of mean (±SD) percent (%) change from baseline in IGA, EASI or Pruritus NRS (linear scale) with that of the mean (±SD) functional dupilumab concentrations in serum (linear scale). Observed data will be used for these analyses.

The concentration-response relationship analyses will be implemented for patients in the PK population with at least one non-missing IGA, EASI, or pruritus NRS value, as applicable for the each concentration-response assessment. Hence, there may be modest differences from the primary efficacy analysis due to the differences in the analysis populations. Patients will be analyzed according to the treatment actually received.

No formal statistical testing will be performed.

[redacted]

6 DATA CONVENTIONS

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

6.1 Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of NRS is defined in Section 4.4.2. The following rules specify the determination by both date/time information:

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

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

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen- failure patient ID or enrolled patient ID.

6.2 General Data Handling Conventions

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

6.3 Data Handling Convention Missing Data

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

Adverse event

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

Adverse event start date

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

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month, then impute AE

start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

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

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

Adverse event end date

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

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

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

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

Medication start and end date missing

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

Prior medication start date

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

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

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

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

Prior medication end date

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

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

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

Concomitant medication start date

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

Concomitant medication end date

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

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

If end year is missing: Impute date using the end of last study visit date. Imputation flag is 'Y'.

Medication coding

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

PCSA

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

6.4 Analysis Visit Window

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG, ADA) will be summarized by the study scheduled visits described Appendix 10.2, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT/EOS visits, based on the study day:

Time window for efficacy variables

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days		
			IGA, EASI, BSA, POEM, DLQI	EQ-5D	Sick-Leave/Missed School Days
1	Screening	<1	<1		
2	Baseline	1	1	≤1	≤1
3	Week 2	15	[2,22]		
4	Week 4	29	[23, 43]		[2, 43]
5	Week 8	57	[44, 71]	[2, 85]	[44, 71]
6	Week 12	85	[72, 99]		[72, 99]
7	Week 16 (End of Treatment)	113	[100, 127]	[86, 155]	[100, 127]
8	Week 20	141	[128, 155]		[128, 155]
9	Week 24	169	[156, 183]		[156, 183]
10	Week 28 (End of Study)	197	≥184	≥156	≥184

*Study days are calculated from 1st day of dupilumab injection (1st day of randomization if the patient is not treated)

Time window for safety variables

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days						
			Vital Signs	Weight	ECG	Hematology and Chemistry	Urinalysis	Serum Pregnancy Test	Urine Pregnancy Test
1	Screening	<1	<1	<1	<1	<1	<1	<1	
2	Baseline	1	1	1		1	1		≤1
3	Week 2	15	[2,22]						
4	Week 4	29	[23, 43]						[2, 43]
5	Week 8	57	[44, 71]			[2, 85]			[44, 71]
6	Week 12	85	[72, 99]						≥72

7	Week 16 (End of Treatment)	113	[100, 127]	[86, 155]	[86, 155]	[86, 155]	[2, 155]	[2, 155]	
8	Week 20	141	[128, 155]						
9	Week 24	169	[156, 183]						
10	Week 28 (End of Study)	197	≥184	≥156	≥156	≥156	≥156	≥156	

*Study days are calculated from 1st day of dupilumab injection (1st day of randomization if the patient is not treated)

Time window for other variables

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days	
			[redacted]	PK/Drug Concentration, ADA
1	Screening	<1	<1	
2	Baseline	1	1	≤1
3	Week 2	15		
4	Week 4	29		
5	Week 8	57		
6	Week 12	85		[2, 99]
7	Week 16 (End of Treatment)	113	[2, 155]	[2, 155]
8	Week 20	141		
9	Week 24	169		
10	Week 28 (End of Study)	197	≥156	≥156

*Study days are calculated from 1st day of dupilumab injection (1st day of randomization if the patient is not treated)

In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) or end of study (EOS), whichever comes first if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ETV/EOT/EOS are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSA values from laboratory, vital sign or ECG as well as the baseline values.

For the ePRO data collected daily, the analysis visit windows will be implemented following the procedures below:

Step 1: Derive the study day,

- If diary date $\geq 1^{st}$ injection date, then diary study day=diary date – 1st injection date +1;
- Otherwise diary study day=diary date – 1^{st} injection date

Randomization date will be used instead of 1^{st} injection date for patients randomized but not treated.

Step 2: Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc, with 7 days interval between visit windows.

7 INTERIM ANALYSIS

No interim analysis is planned.

Sponsor may run a first step analysis when all patients complete their 16-week treatment period.

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.

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

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;140:1513-9.

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

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.

Kaufmann R, Bieber T, Helgesen AL, Andersen BL, Luger T, Poulin Y, et al. Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: a randomized trial. Allergy. 2006;61:375-81.

Zhuo L, Xu L, Ye J, Sun S, Zhang Y, Burstrom K, et al. Time Trade-Off Value Set for EQ-5D-3L Based on a Nationally Representative Chinese Population Survey. Value in Health. 2018;21(11):1330-7.

10 APPENDIX

10.1 Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16	ITT population	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test on observed value or LOCF, and on PP population	Yes	Line plot, forest plot
Secondary continuous variables	ITT population	MI	MMRM, ANCOVA with LOCF	Yes for EASI and NRS endpoints	Line plot
Secondary categorical variables	ITT population	Cochran-Mantel-Haenszel test / define missing as treatment failure	Cochran-Mantel-Haenszel test / LOCF	Yes for EASI and NRS endpoints	Line plot, forest plot

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	Safety population	Descriptive statistics	No	No	No
Laboratory Measures	Safety population	Descriptive Statistics	No	No	No
Vital sign	Safety population	Descriptive Statistics	No	No	No
Physical Examination	Safety population	Descriptive Statistics	No	No	No
ECG	Safety population	Descriptive Statistics	No	No	No

10.2 Schedule of Events

Study Procedure	SCR	RND	Treatment							EOT	Follow-up		EOS	Unscheduled visit[a] (if applicable)	Early termination (if applicable)
VISIT(V)	V1	V2	V3	V4		V5		V6		V7	V8	V9	V10		
Week(W)		W0	W2	W4	W6	W8	W10	W12	W14	W16	W20	W24	W28		
Day (D)	D-7 to D-35	D1	D15	D29	D43	D57	D71	D85	D99	D113	D141	D169	D197		
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Screening/baseline															
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Medical history/ demographics	X														
Randomization		X													
Training on pruritus reporting system[b]	X														
Treatment															
Injection training/observation		X	X	X		X		X							
Administer IMP[c]		X	X	X	X	X	X	X	X						
Dispense/review patient dosing diary[d]				X		X		X		X					
IMP dispensation/account[e]				X		X		X		X					
Con meds/procedures	X	X	X	X		X		X		X	X	X	X	X	X
Efficacy[f,g]															
Pruritus NRS (daily)[b]	X	X	X	X		X		X		X	X	X	X	X	X
Pruritus categorical scale (daily)[b]	X	X	X	X		X		X		X	X	X	X	X	X
POEM, DLQI[h]	X	X	X	X		X		X		X	X	X	X	X	X
EQ-5D[h]		X				X				X			X		X
IGA, EASI, BSA	X	X	X	X		X		X		X	X	X	X	X	X
Assess sick-leave/missed school days		X		X		X		X		X	X	X	X	X	X
Photograph AD area (selected sites)[i]		X								X			X	X	X

Study Procedure	SCR	RND	Treatment							EOT	Follow-up		EOS	Unscheduled visit[a] (if applicable)	Early termination (if applicable)
VISIT(V)	V1	V2	V3	V4		V5		V6		V7	V8	V9	V10		
Week(W)		W0	W2	W4	W6	W8	W10	W12	W14	W16	W20	W24	W28		
Day (D)	D-7 to D-35	D1	D15	D29	D43	D57	D71	D85	D99	D113	D141	D169	D197		
Visit Window (d)			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Safety[f]															
Weight	X	X								X			X	X	X
Height	X														
Vital signs	X	X	X	X		X		X		X	X	X	X	X	X
Physical examination[j]	X									X			X		X
Electrocardiogram	X									X			X		X
Adverse events	X	X	X	X		X		X		X	X	X	X	X	X
Laboratory Testing[f]															
HIV ab, HBsAg, HbsAb, HBcAb[k], and Hep C Ab[k]	X														
Hematology and chemistry	X	X				X				X			X	X	X
Urinalysis	X	X								X			X	X	X
Pregnancy test (WOCBP only)	Serum	Urine		Urine		Urine		Urine		Serum			Serum	Urine	Serum
[redacted]	[redacted]	[redacted]								[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]								[redacted]				[redacted]	[redacted]
[redacted]		[redacted]													
ANA, anti-dsDNA (if ANA positive)	X														
PK/Drug Concentration and ADA Samples[f]															
Functional dupilumab PK sample		X						X		X			X	X	X
Anti-dupilumab antibody sample		X						X		X			X	X	X

Abbreviations: AD = atopic dermatitis, ADA = anti-drug antibody, ANA = anti-nuclear antibody, anti-dsDNA = anti-double-strand DNA, BSA = body surface area, DLQI = Dermatology Life Quality Index, EASI = Eczema Area and Severity Index, EQ-5D = EuroQol five dimensions questionnaire, EOS = end-of-study, EOT = end-of-treatment, HBcAb = hepatitis B core antibody, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, Hep C Ab = hepatitis C antibody, HIV ab = human immunodeficiency virus antibody, IGA = investigator global assessment, [redacted], IMP = investigational medicinal product,
NRS = numerical rating scale, PK = pharmacokinetics, POEM = Patient Oriented Eczema Measure, RND = randomization, SCR = screening, [redacted], WOCBP = woman of child bearing potential.

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

b Patients will be trained at the screening visit on using the appropriate diary system to report pruritus daily and provide other information as required. Investigators will check patients' reports at each visit.

c Patients will be monitored at the study site for a minimum of 30 minutes after the IMP administration for any signs or symptoms of a hypersensitivity reaction. Adverse event assessments will be done at 30 minutes (±10 minutes) post-injection.

d For patients who choose to self-administer the IMP at Weeks 6, 10, and 14, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

e For patients who choose to self-administer the IMP, the IMP will be dispensed to the patient for the dose that will be administered before the next clinic visit. Patients will return the original kit box for the prefilled syringe at each clinic visit.

f To be collected before the injection of the IMP.

g Assessments/procedures should be conducted in the following order: patient reported outcomes (PROs), Investigator assessments, safety and laboratory assessments, and then administration of the IMP.

h All questionnaires will be administered before any invasive procedures (blood draws, IMP injection, etc).

i Selected sites only - photograph AD area

j If patients have any symptom or sign of ocular surface diseases, eg, conjunctivitis and blepharitis, at screening or during study period, ophthalmological examinations should be done.

k Heptitis B virus (HBV) DNA testing should be performed during screening period for patients presenting with HBsAg (-) and HBcAb (+). In case of results showing HCV Ab positive, an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the patient is a false positive.

[redacted]

10.3 Criteria for Treatment-Emergent Potentially Clinical Significant Abnormality (PCSA) for Dupilumab AD studies

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

Parameter	Treatment Emergent PCSA	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.

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-0.0766;
if eqq1cd=3    then eq5d=eq5d-0.2668;
********Self-care**********;
if eqq2cd=2    then eq5d=eq5d-0.0441;
if eqq2cd=3    then eq5d=eq5d-0.2912;
******Usual activities*****;
if eqq3cd=2    then eq5d=eq5d-0.0370;
if eqq3cd=3    then eq5d=eq5d-0.0538;
*****Pain/discomfort******;
if eqq4cd=2    then eq5d=eq5d-0.0274;
if eqq4cd=3    then eq5d=eq5d-0.0409;
*****Anxiety/depression*****;
if eqq5cd=2        then eq5d=eq5d-0.0359;
if eqq5cd=3        then eq5d=eq5d-0.1771;

if (eqq1cd=. or eqq2cd=. or eqq3cd=. or eqq4cd=. or eqq5cd=.)
                        then eq5d=.;
run;
```

10.5 Search Criteria for TEAE of Special Interest/TEAE Syndrome

AESI	Search Criteria
Anaphylactic reactions	Narrow SMQ for "anaphylactic reaction" *Note: CMQsn00021*
Systemic or extensive hypersensitivity reaction	Narrow SMQ for "hypersensitivity" *Note: CMQsn00214*
Malignancy	Narrow SMQ for "Malignancy" *Note:CMQsn00090*
Helminthic infections	HLGT as "Helminthic disorder" *Note: CMQ10544*
Suicide-related events	Narrow SMQ for "Depression and suicide/self-injury" *Note: CMQsn00035*
Blepharitis (severe or serious or lasting ≥4 weeks)	HLT as "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events CRF page or lasting ≥28 days *Note: CMQ10497*
Any type of conjunctivitis (severe or serious or lasting ≥4 weeks)	Selected PTs and "Severe" ticked in Adverse Events CRF page or lasting ≥28 days *Note: CMQ10498*
Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP	"Pregnancy" or "Partner Pregnancy" checked on the Pregnancy CRF page as reported by the investigator
Symptomatic overdose (serious or nonserious) with IMP/NIMP	"Symptomatic overdose" checked as "Yes" on the Overdose CRF page as reported by the investigator

10.6 Search Criteria for Personal history of atopic/allergic conditions

Atopic/allergic conditions	Search Criteria
Atopic Dermatitis	PT as "Dermatitis atopic"
Asthma	Include the following PTs: -Asthma -Asthma exercise induced -Bronchospasm -Status asthmaticus -Asthmatic crisis -Bronchial hyperreactivity -Reactive airways dysfunction syndrome -Aspirin-exacerbated respiratory disease -Childhood asthma *Note: CMQ10424*
Allergic Conjunctivitis	Include the following PTs: -Conjunctival irritation -Conjunctival oedema -Conjunctival ulcer -Conjunctivitis -Conjunctivitis allergic -Giant papillary conjunctivitis -Inclusion conjunctivitis -Ophthalmia neonatorum -Seasonal allergy -Conjunctival hyperaemia -Inclusion conjunctivitis neonatal -Pingueculitis -Acute haemorrhagic conjunctivitis -Ligneous conjunctivitis -Noninfective conjunctivitis *Note: CMQ10539*
Atopic Keratoconjunctivitis	PT as "Atopic Keratoconjunctivitis" and "Keratoconjunctivitis" *Note: CMQ10538*
Allergic Rhinitis	HLT= "Nasal congestion and inflammations" exclude PT= "Radiation rhinitis" *Note: CMQ10540*
Chronic Rhinosinusitis	Include the following PTs: -Chronic sinusitis -Chronic hyperplastic eosinophilic sinusitis -Chronic eosinophilic rhinosinusitis -Chronic rhinosinusitis with nasal polyps *Note: CMQ10440*
Nasal Polyps	Include the following PTs: -Nasal polyps -Sinus polyp -Sinus polyp degeneration -Chronic rhinosinusitis with nasal polyps *Note: CMQ10522*
Eosinophilic Esophagitis	PT as "Eosinophilic oesophagitis" *Note: CMQ10541*

Food Allergy	Include the following PTs: -Flour sensitivity -Food allergy -Milk allergy -Reaction to food additive -Allergy to fermented products -Caffeine allergy -Transplantation associated food allergy -Gluten sensitivity *Note: CMQ10537*
Hives	HLT as "Urticarias" *Note: CMQ10458*
Other Allergies	HLGT as "Allergic conditions" exclude above allergic conditions *Note: CMQ10523 exclude above allergic conditions*

10.7 List of efficacy-related entry criteria

I 03. EASI score ≥16 at the screening and baseline visits

I 04. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits

I 05. ≥10% BSA of AD involvement at the screening and baseline visits

I 06. Baseline Pruritus NRS average score for maximum itch intensity ≥4

NOTE: Baseline Pruritus NRS average score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 35-day maximum duration for screening

E 03. Having used any of the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the Investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment:

- Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, and methotrexate)
- Phototherapy for AD

E 04. Treatment with TCS or TCI within 1 week before the baseline visit

E 05. Treatment with systemic TCM within 4 weeks before the baseline visit or treatment with topical TCM within 1 week before the baseline visit

E 06. Treatment with biologics as follows:

- Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit or until lymphocyte count returns to normal, whichever islonger
- Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer

E 07. Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit)

E 08. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit

E 09. Planned or anticipated use of any prohibited medications (see protocol Section 8.8.1) and procedures during study treatment