1.2 STUDY FLOW CHART

Table 1 - 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]															
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.

IL-4Rα:	IL-4 receptor alpha
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
ISR:	injection site reaction
ITT:	intent-to-treat
LDH:	lactate dehydrogenase
LOCF:	last observation carried forward
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	multiple imputation
MMRM:	mixed-effect model repeated measures
NIMP:	noninvestigational medicinal product
NRS:	numerical rating scale
PCP:	pneumocystis pneumonia
PCSA:	potentially clinically significant abnormality
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
SC:	subcutaneous
SIT:	allergen-specific immunotherapy
SOC:	system organ class
SUSAR:	suspected unexpected adverse drug reaction
TARC:	thymus and activation regulated chemokine
TB:	tuberculosis
TCI:	topical calcineurin inhibitors
TCM:	Traditional Chinese Medicine
TCS:	topical corticosteroids
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
WBC:	white blood cell
WOCBP:	woman of childbearing potential

disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects or safety risks). The design is similar to global pivotal studies, R668-AD-1334 and R668-AD-1416. The primary objective is to demostrate the efficacy of dupilumab (300 mg q2w) monotherapy, assessed by proportion of patients with both an IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 comparing with placebo. 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.

4.2.2 Rationale for Dose Selection

The dose regimen of SC dupilumab selected for this study is 300 mg q2w. All patients randomized to receive treatment with dupilumab will get an initial loading dose of 600 mg on Day 1. The administration of the loading dose of dupilumab will allow systemic concentrations to reach steady-state faster and potentially reduce the time to onset of clinical effect.

The doses of dupilumab in this study were based on the efficacy and safety results from global pivotal Phase 3 studies (R668-AD-1334 and R668-AD-1416). Dupliumab phase 3 studies have shown that dupilumab dose regimens (300 mg qw and 300 mg q2w) result in statistically significant, clinically meaningful improvements in objective signs, subjective symptoms, mental health, and QOL in patients with moderate-to-severe AD. These 2 dose regimens were very similar when used as a monotherapy, with no meaningful differences observed in the response rate of the 300 mg qw regimen over the 300 mg q2w regimen during the 16-week treatment period.

These clinical data indicate that 300 mg q2w is adequate for patients with moderate-to-severe AD to help them reach their maximal response.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

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 includes 16-week treatment period and 12-week follow-up.

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 in a 1:1 ratio 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). Randomization will be stratified by baseline disease severity (moderate [IGA 3] versus severe [IGA 4] AD); details will be specified in the interactive response technology (IRT) specifications document. 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 IMP will be administered 300 mg at Weeks 2, 4, 6, 8, 10, 12, and 14 (Figure 1). 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 ADA, and clinical assessments will be performed at specified clinic visits as noted in the Schedule of Events (Table 1).

The end of treatment visit will occur at Week 16, 2 weeks after the last dose of the IMP. 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.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Each patient will experience 7 to 35-day screening, 16-week treatment and 12-week follow-up period. The total study duration will be up to 33 weeks.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur when the last patient who has completed the 12-week follow-up period. The end of the clinical trial is defined as the last patient's last visit.

6.2.2.1 Premature termination of the study

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

6.2.2.2 Close-out of a site

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

Investigator's decision

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

Sponsor's decision

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

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

In all cases, the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEES

Not applicable.

8.1.4.2 Investigational medicinal product discontinuation

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. The reasons for temporarily or permanently discontinuation of the IMP are described in Section 10.3.

Patients who opt to withdraw from the study will be asked to complete study assessments, per Section 10.1.5.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

8.2.1 Background treatment

All patients are required to apply moisturizers (emollients) at least twice daily for at least 7 days before randomization and to continue the treatment throughout the study (all 28 weeks where applicable). However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of nonlesional skin designated for such assessments for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study. Patients may continue using stable doses of such moisturizers if initiated before the screening visit.

8.2.2 Rescue treatment

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD with otherwise prohibited medications or procedure (see Section 8.8.1) may be provided to study patients at the discretion of the Investigator. Please refer to the label of the product for the usage of rescue treatment. For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous, and genital areas. 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.

- 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

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

Questionnaires and patient-reported assessments will be administered prior to obtaining Investigator assessments, safety and laboratory assessments, and IMP administration. Please see the user guidance on the administration and use of all patient reported instruments (including POEM, DLQI, and EQ-5D).

9.2.1.1 Eczema area and severity index

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (10). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity by the Investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

9.2.1.2 Patient assessment of pruritus: numerical rating scale

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a 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.

than there might be with a 5-point scale (13). 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 pruritus categorical scale 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.

9.2.1.8 Sick Leave/Missed School Days

Patients who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment. Patients will undergo this assessment at time points according to Section 1.2.

The assessment tool is provided in the user guidance.

9.2.1.9 Atopic Dermatitis Area Photographs

At selected study sites, photographs will be taken of a representative area of AD involvement (eg, the lesional area used for EASI assessments on Day 1/baseline [pre-dose]). Subsequent photographs of the same area will be taken at Week 16 (end of treatment) and Week 28 (end of study).

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

9.2.2 Safety endpoints

9.2.2.1 Adverse events

Refer to Section 10.4 to Section 10.6 for details.

9.2.2.2 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 to measure overall patient health at screening. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population.

Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Blood samples should be collected after a 6 to 8 hour fast, if possible; fasting is not mandatory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to Section 1.2. Tests will include

- Blood chemistry: sodium, potassium, chloride, carbon dioxide, calcium, glucose, albumin, total protein (serum), creatinine, blood urea nitrogen, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, uric acid, 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: hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs) and differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils), red cell indices, platelet count
- Urinalysis: Color, clarity, pH, specific gravity, ketones, protein, glucose, blood, bilirubin, leukocyte esterase, nitrite, WBC, RBC, hyaline and other casts, bacteria, epithelial cells, crystals, yeast
  Microscopic analysis will only be done in the event of abnormal dipstick results.
- Pregnancy testing (serum or urine) will be performed for all women of childbearing potential.
- Testing for HIV antibody, HBsAg, HBsAb, HBcAb, HBV DNA (for patients presenting with HBsAg [-] and HBcAb [+]) and hepatitis C antibody, and ANA will be performed at screening
  Hepatitis C virus (HCV) RNA testing may be performed to rule out a false positivity, if the Investigator believes the patient is a false positive. Anti-dsDNA antibody will be tested if ANA is positive.

9.2.2.3 Vital Signs

Vital signs, including heart rate, blood pressure, body temperature, and respiration rate, will be collected.

9.2.2.4 Physical examination

A thorough and complete physical examination will be performed at time points according to Section 1.2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history. 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.

9.2.2.5 Weight and Height

Weight and height will be determined at time points according to Section 1.2.

[redacted]

9.4 FUTURE USE OF SAMPLES

Not applicable.

9.5 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in this study are standard for the evaluation of therapy in patients with AD.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

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

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

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

10.1.1 Visit 1/Screening/Day -7 to -35

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

- Inclusion/exclusion
- Medical history and concurrent illnesses
- Demographics
- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Training on the pruritus reporting system
- Pruritus NRS and pruritus categorical scale
- All questionnaires will be administered before any invasive procedures
  - Patient oriented eczema measure (POEM)
  - Dermatology life quality index (DLQI)
- Vital signs
- IGA
- EASI
- BSA involvement of AD
- Weight
- Height
- Physical examination (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.)
- ECG

- Laboratory testing:
  - HIV ab
  - HBsAg, HBsAb, HBcAb, HBV DNA testing should be done for patients presenting with HBsAg (-) and HBcAb (+)
  - Hepatitis C antibody (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)
  - Hematology and chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - [redacted]
  - Anti-nuclear antibody (ANA)
  - Anti-dsDNA (only for ANA positive patients)

10.1.2 Treatment Period

10.1.2.1 Visit 2/Baseline/Day 1 (Randomization)

The following information will be collected:

- Inclusion/Exclusion
- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS and pruritus categorical scale
- All questionnaires will be administered before any invasive procedures:
  - POEM
  - DLQI
  - EQ-5D
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- BSA
- Photograph AD area (select sites only)
- Weight
- Laboratory testing:
  - Hematology and chemistry
  - Urinalysis
  - Urine pregnancy test (WOCBP only)

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the e-CRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories and patient electronic diary will be considered source data.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal products

Temporary treatment discontinuation may be considered by the Investigator because of AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator considers, according to his/her best medical judgment, that the AE is sufficiently resolved and unlikely to recur after resuming therapy with the IMP.

The following conditions(s) will be causes for temporary treatment discontinuation:

- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix E
- Other intercurrent illnesses or major surgery
- Infections or infestations that do not respond to medical treatment
  The IMP should be discontinued until the infection is resolved.
- Treatment with prohibited concomitant medication or procedure as described in Section 8.8.1

After the lab abnormality leading to suspension of dosing normalizes sufficiently, the IMP may be resumed at the discretion of the principal Investigator in consultation with the sponsor. Similarly, the IMP may be resumed after the medication leading to suspension of dosing is discontinued. A decision to discontinue the IMP and/or to reinstitute the IMP should be discussed with the sponsor. The Investigator may suspend the IMP at any time, even without consultation with the sponsor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the sponsor should be contacted as soon as possible in any case of the IMP discontinuation. Resumption of study treatment after temporary discontinuation should always be discussed with the sponsor.

10.4.1.3 Adverse event of special interest

An 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.

For these AESIs, the sponsor will be informed immediately (ie, within 24 hours), per SAE notification described Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

- 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 subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2)
  - In the event of pregnancy in a female participant, IMP should be discontinued
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose within the intended therapeutic interval (eg, 11 days for dupilumab). The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.

  Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 General guidelines for reporting adverse events

All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her

opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).

The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the sponsor. Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.

When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.

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

Instruction for AE reporting timeframes are summarized in Table 2.

Table 2 - Summary of adverse event reporting instructions

Event category	Specific events	Reporting timeframe
Adverse event (non-SAE, non-AESI)	Any AE that is not SAE or AESI	Routine
Serious adverse event	Any AE meeting seriousness criterion per Section 10.4.1.2	Expedited (within 24 hours)
Adverse event of special interest	Anaphylactic reactions	Expedited (within 24 hours)
	Systemic or extensive hypersensitivity reactions	Expedited (within 24 hours)
	Malignancy	Expedited (within 24 hours)
	Helminthic infections	Expedited (within 24 hours)
	Suicide-related events	Expedited (within 24 hours)
	Blepharitis (severe or serious or lasting ≥4 weeks)	Expedited (within 24 hours)
	Any type of conjunctivitis (severe or serious or lasting ≥4 weeks)	Expedited (within 24 hours)
	Pregnancy of a female subject or a female partner of a male subject	Expedited (within 24 hours)
	Symptomatic overdose	Expedited (within 24 hours)

Abbreviations: SAE: serious adverse event; AESI: adverse event of special interest

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.

- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix E.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices:

- Neutropenia
- Thrombocytopenia
- Increase of ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the sponsor will report in an expedited manner:

- All SAEs, that are both unexpected and at least reasonably related to the IMP suspected unexpected adverse drug reactions (SUSARs), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs, that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (please refer to the Investigator's Brochure [IB]).

Any other AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

For safety, the treatment code will be unblinded by the sponsor for reporting to the Health Authority of any SUSAR and reasonably associated with the use of the IMP according to the judgment of the Investigator and/or the sponsor.

In case of a SUSAR, Sanofi Global Pharmacovigilance and Epidemiology will utilize XGRID to reveal medication assignment for regulatory reporting requirements for the particular case.

The sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

Allergic reaction is a risk associated with the administration of most therapeutic monoclonal antibodies, including dupilumab.

Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients, during or shortly after the pharmacologic or biologic agent is given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of infusion reaction, but these events may also occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other immune-mediated mechanisms (eg, cytokine-mediated). Allergic reactions may begin within a few hours and persist up to 24 hours postdosing. Refer to Appendix C "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored for at least 30 minutes after each injection of the IMP at study site for any signs or symptoms of a hypersensitivity reaction. Any anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment are AESI (report within 24 hours) and study medication should be permanently discontinued. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 30 minutes after administration.

10.6.2 Severe injection site reactions

Based on the SC mode of administration of a therapeutic protein, severe injection site reactions are considered as a potential risk. Patients who experience an injection site reaction must be closely monitored for the possibility of a more intense injection site reaction with a future injection.

11 STATISTICAL CONSIDERATIONS

This section provides the basis for the SAP for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked. Analysis variables are listed in Section 9.

11.1 DETERMINATION OF SAMPLE SIZE

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.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who signed the informed consent.

Randomized patients consist of all patients, who have been allocated a treatment kit based on a randomization process. For studies using IRT for drug allocations, it will consist of all patients with a treatment kit number allocated and recorded in the IRT database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy population

Efficacy analyses will be based on the ITT population which includes all randomized patients. Patients will be analyzed according to the treatment allocated by the IRT at randomization (as randomized).

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

- For the binary efficacy endpoints, if rescue medication or procedure is used (see Section 8.2.2 for rescue), the patient will be specified as a non-responder from the time the rescue is used.
- If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal.

The primary efficacy analyses will be performed on the PP population as a supportive analysis.

Sensitivity analysis using last observation carried forward (LOCF) approach to determine patient's status at Week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data.

In addition, the Cochran-Mantel-Haenszel method adjusted by randomization strata will also be performed on the observed response regardless of rescue medication or procedure use, and patients with missing values will be counted as non-responders.

11.4.3.2 Analyses of secondary efficacy endpoints

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

The continuous endpoints will be analyzed using the MI with ANCOVA model as the primary analysis. Patients' efficacy data after rescue medication up to Week 16 will be set to missing and then imputed by the MI method. Missing data will be imputed 50 times to generate 50 complete data sets by using the SAS MI procedure (using Markov Chain Monte Carlo method). 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 on the efficacy effect:

- Continuous efficacy endpoints: 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, this patient will be counted as a non-responder for endpoints after withdrawal.

The mixed-effect model repeated measures (MMRM) will be used to assess the robustness of the analysis with regards to handling of missing data. The MMRM model includes factors (fixed effects) for treatment, randomization strata, visit, treatment-by-visit interaction, and relevant baseline values. It will provide baseline adjusted least-squares means at Week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p values for treatment comparisons.

There will be other sensitivity analyses using MI method based on all observed data regardless if rescue treatment is used or if data are collected after withdrawal and using LOCF method. Additional details will be provided in the SAP.

11.4.3.3 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 testing hierarchy will be detailed in the SAP.

11.4.4 Analyses of safety data

The summary of safety results will be presented by treatment group. All safety analyses (includes reported TEAEs and other safety information as clinical laboratory evaluations, vital signs, and 12-lead ECG results) will be performed on the safety population using the following common rules:

- The baseline value is defined generally as the last available value before randomization.

For safety variables, two observation periods are defined:

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

The following definitions will be applied to clinical laboratory evaluations, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, vital signs, and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

TEAEs leading to* permanent *treatment discontinuation:

Number (%) of patients with at least one TEAE leading to permanent treatment discontinuation will be summarized by treatment group and presented by primary SOC (sorted by internationally agreed order), HLGT, HLT, and PT sorted in alphabetical order. TEAE leading to permenant treatment discontinuation will be listed by treatment group and patient.

Adverse events of special interest:

Treatment-emergent AESI will present number (%) of patients overall, by AESI category and PT, sorted by decreasing incidence of PT within each AESI category.

11.4.4.2 Clinical laboratory evaluations

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

Number and percentage of patients with a treatment-emergent PCSA will be summarized for each clinical laboratory test.

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

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

11.4.4.3 Vital signs

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

Number and percentage of patients with a treatment-emergent PCSA will be summarized for each vital sign variable.

11.4.4.4 Analysis of anti-drug antibody variables

The ADA variables described in Section 9.2.2.7 will be analyzed using descriptive statistics. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

11.4.5 Analysis of pharmacokinetic variables

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
- Correlation analyses:
  - Body weight versus serum concentrations
  - Serum concentrations versus clinical outcomes

No formal statistical analysis will be performed.

11.4.6 Analysis of quality of life and health economics variables

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

[redacted]

[redacted]

11.4.8 Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- 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.

General rules for handling missing data:

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

Unscheduled assessments:

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

11.5 INTERIM ANALYSIS

No interim analysis is planned.

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]

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

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

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 IFN-γ, are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response.

The goal in treating AD is reducing skin inflammation. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids (TCS) are overwhelmingly the most frequently prescribed class of drugs. However, long-term application of TCS is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, hypothalamic pituitary axis effects, and Cushing’s disease). 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 too 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 (3) 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

5 STUDY OBJECTIVES

5.1 PRIMARY

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.

5.2 SECONDARY

- 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 PROs
- To evaluate dupilumab immunogenicity

5.3 OTHER OBJECTIVES

- To evaluate dupilumab systemic exposure
- [redacted]

7 SELECTION OF PATIENTS

The study population consists of adults with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects or safety risks).

7.1 INCLUSION CRITERIA

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

I 01. Male or female, 18 years or older

I 02. Atopic dermatitis (according to American Academy of Dermatology Consensus Criteria, 2014) (1) that has been present for at least 3 years before the screening visit

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

I 07. Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks);

NOTE:

- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 = clear to 2 = mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever is shorter.
- Patients with documented systemic treatment for AD, of sufficient dose and duration, in the past 6 months are also considered as inadequate responders to topical treatments

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched 2 mL prefilled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab/placebo) glass prefilled syringes will be prepared such that the IMPs are identical and indistinguishable, and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by the sponsor.

In accordance with the double-blind design, study patients, Investigators, and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and the reason for code breaking.

Subject withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the subject will be withdrawn from treatment. See Section 10.3.4 for the handling of patients after permanent treatment discontinuation. However, if the emergency unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the subject will not be withdrawn from treatment.

At the facilities where the systemic drug concentration measurements, ADA, and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

[redacted]

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

A total of 160 patients will be randomized on Day 1 in a 1:1 ratio to receive q2w SC injections of 300 mg dupilumab, or matching placebo for 16 weeks. Patients will be randomized to a treatment group according to a central randomization scheme provided by an IRT to the designated site personnel or clinical staff members. Randomization will be stratified by disease severity (IGA 3 versus IGA 4); details will be specified in the IRT specifications document and will be documented in the clinical study report.

9.2.1.3 Body surface area involvement of atopic dermatitis

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

9.2.1.4 Patient-reported dermatology life quality index

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL (11). The format is a simple response (0 to 3, where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL.

9.2.1.5 Patient oriented eczema measure

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (12). 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.

9.2.1.6 Patient-assessed EQ-5D

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

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

9.2.1.7 Patient-assessed pruritus categorical scale

The pruritus categorical scale is a 4-point scale used to assess symptoms that has been used in clinical studies of AD and there is less of a tendency for patients to provide an "average" response

9.2.2.6 ECG

Electrocardiograms will be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Section 1.2. The ECG strips or reports will be retained with the source documentation, and the results will be documented in the electronic case report form (eCRF).

9.2.2.7 Immunogenicity

Anti-drug antibody measurements:

Samples for ADA assessment will be collected at time points listed in Section 1.2.

Anti-drug antibody variable definition:

- 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 (defined as 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 (defined as treatment-emergent response with only the last collected sample positive in the ADA assay)
  - Transient (defined as 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 titer value category definition:

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

All samples that are positive in the ADA assay will be further tested for the presence of anti-dupilumab neutralizing antibodies.

Descriptive statistics for the incidence of anti-dupilumab antibodies response variables will be summarized for the ADA population. Listings of anti-dupilumab antibody status, neutralizing status, and titers per time point and treatment group will be provided.

- Functional dupilumab pharmacokinetic (PK) sample
- Anti-dupilumab antibody sample

- Randomization
- Administer the IMP after all the other assessments have been performed. Train patient/caregiver in injection technique if the patient chooses to self-administer the IMP at selected weeks.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection for any signs or symptoms of a hypersensitivity reaction. In addition to the predose assessments, AE assessments will be done at 30 minutes (±10 minutes) postinjection.

10.1.2.2 Visit 3/Week 2/Day 15 (±3 days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS and pruritus categorical scale
- All questionnaires will be administered before any invasive procedures:
  - POEM
  - DLQI
- Vital signs
- IGA
- EASI
- BSA
- Administer the IMP after all the other assessments have been performed. Train patient/caregiver in injection technique if the patient chooses to self-administer the IMP at selected weeks.
  - The patient will be monitored in the clinic for at least 30 minutes after the injection for any signs or symptoms of a hypersensitivity reaction. In addition to the predose assessments, AE assessments will be done at 30 minutes (±10 minutes) postinjection

10.1.2.3 Visit 4/Week 4/Day 29 (±3 days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS and pruritus categorical scale

10.3.2 Permanent treatment discontinuation with investigational medicinal products

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to reexpose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the CRF or e-CRF.

Patients must be withdrawn from the treatment (ie, from any further IMP administration) for the following reasons:

- At their own request or at the request of their legally authorized representative (Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- At the specific request of the sponsor
- In the event of a protocol deviation, at the discretion of the Investigator or the sponsor
- Any code broken requested by the Investigator will lead to permanent treatment discontinuation.
- Pregnancy
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Any opportunistic infection or other infections whose nature or course may suggest an immunocompromised status (see Appendix D)
- Serum ALT >3 ULN and total bilirubin >2 ULN (see Appendix E)
- Serum ALT >5 ULN if baseline ALT <2 ULN or ALT >8 ULN if baseline ALT >2 ULN (see Appendix E)
- Certain AEs deemed related to the IMP (eg, severe and prolonged injection site reactions)

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

10.6.3 Infections, including parasitic infections

Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding and activation of their respective receptors, it inhibits the Th2 cytokines productions. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The Th2 response is characterized by production of IL-4 and IL-5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore, patient with treatment of dupilumab may potentially have an increased risk of helminthic parasitic infection

In order to minimize this risk, any patient with an active parasitic infection should be excluded from the study. Similarly, patients with suspected parasitic infection, or those at high risk of parasitic infection are also excluded, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue, and hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors). Subsequent medical assessments (eg, stool exam, blood tests) must be performed in order to rule out parasitic infection/infestation.

Helminthic infections defined in Section 10.4.1.3 should be reported as AESIs within 24 hours.

A complete diagnostic work-up should be performed (ie, cultures, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment.

Infections or infestations that do not respond to medical treatment should have the IMP discontinued until the infection is resolved.

For any opportunistic infection or other infections, whose nature or course may suggest an immunocompromised status (see Appendix D), patients MUST be permanently discontinued from the IMP.

10.6.4 Elevated liver function tests

No pre-clinical and clinical data suggested any hepatic toxicity of anti-IL4 agent; however, as general consideration of clinical development, the administration of immunosuppressant or immunomudulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow potential liver abnormalities, assessment of total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing (see Section 9.2.2.2). Clinical

The PP population includes all patients in the ITT population except for those who are excluded because of major efficacy-related protocol violations. A major protocol violation is one that may affect the interpretation of study results. The criteria of major protocol deviations are defined as the following:

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

11.3.2 Safety population

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

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 analysis population.

11.3.3 Other analysis populations

The PK population includes all randomized patients with at least 1 post-baseline drug concentration result. The ADA population includes all randomized patients with at least 1 postbaseline ADA result. Patients will be analyzed according to the treatment actually received.

11.4 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.

11.4.1 Demography and Baseline Characteristics

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

No statistical tests will be performed on demographic characteristics.

11.4.4.1 Adverse Events

All Adverse events reported in this study will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) in effect at the time of database lock. The analyses of adverse events will focus on TEAEs.

Definitions

Pretreatment AEs are defined as AEs that developed or worsened during the pre-treatment period.

Treatment-emergent adverse events are defined as AEs that developed or worsened during the treatment-emergent period. The treatment-emergent period is from first administration of IMP to end of the follow-up period.

Treatment-emergent adverse events (TEAE)

The incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an 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 SOC and PT.

Death

The following deaths summaries will be generated:

- 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 treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Listings will be provided for all deaths by treatment group and patient with flags indicating on-treatment status.

Serious adverse events:

Number (%) of patients with at least one treatment emergent SAE will be summarized by treatment group and presented by primary SOC (sorted by internationally agreed order), HLGT, HLT, and PT sorted in alphabetical order. SAEs will also be listed by treatment group and patient.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient’s informed consent must be reviewed and approved by the sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, IB, Investigator’s curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.