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AMENDED CLINICAL TRIAL PROTOCOL NO. 01

COMPOUND: dupilumab/SAR231893

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

STUDY NUMBER: EFC15116

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: dupilumab/SAR231893	STUDY No: EFC15116
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 (AD)
INVESTIGATOR/TRIAL LOCATION	China
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVES	**Primary objective:** The primary objective is to evaluate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD. **Secondary objectives:** • To evaluate the safety of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD. • To evaluate the effect of dupilumab on improving patient reported outcomes (PROs) • To evaluate dupilumab immunogenicity **Other objectives:** • To evaluate dupilumab systemic exposure [redacted]
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD. The study duration 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) 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 one of the following: • Dupilumab 300 mg subcutaneously (SC) once every 2 weeks (q2w), following a loading dose of 600 mg on Day 1, OR • Matching placebo (double the amount of placebo on Day 1 to match the loading dose) SC q2w Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA) = 3] versus severe [IGA = 4] AD). 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. 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. Safety laboratory tests, collection of samples for dupilumab concentrations and anti-drug antibodies (ADA), and clinical assessments will be performed at specified clinic visits.
STUDY POPULATION **Main selection criteria**	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), see below: **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. Eczema Area and Severity Index (EASI) score ≥16 at the screening and baseline visits I 04. Investigator's Global Assessment (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% body surface area (BSA) of AD involvement at the screening and baseline visits I 06. Baseline Pruritus numerical rating scale (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 topical corticosteroids (TCS) of medium to higher potency (± topical calcineurin inhibitors [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 and are potentially eligible for treatment with dupilumab after appropriate washout, subject to approval by the sponsor. - Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the Investigator or by the patient's treating physician. - Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician. If documentation is inadequate, potential patients may be re-screened after such documentation is obtained (ie, patients are shown to fail a 28-day course of medium-to-higher potency TCS [±TCI]).
	I 08. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (NOTE: See E 07 for limitations regarding emollients) (See background treatment with topical emollient inSection 8.2)
	I 09. Willing and able to comply with all clinic visits and study-related procedures
	I 10. Able to understand and complete study-related questionnaires
	I 11. Signed written informed consent
	Exclusion criteria
	E 01. Participation in a prior dupilumab clinical study
	E 02. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
	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, interferon-gamma [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 traditional Chinese medicine (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 is longer - 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 Section 8.8.1) and procedures during study treatment
	E 10.	Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
	E 11.	Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit NOTE: patients may be rescreened after infection resolves
	E 12.	Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or unusually frequent, recurrent, or prolonged infections, per Investigator's judgment
	E 13.	Active tuberculosis (TB), latent untreated TB, or a history of potentially incompletely treated TB or non-TB mycobacterial infection, unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing would be performed according to local guidelines if required by regulatory authorities or ethics commitees
	E 14.	History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
	E 15.	Active hepatitis or patients with positive hepatitis B surface antigen (HBsAg), or patients with positive hepatitis B core antibody (HBcAb) plus positive hepatitis B virus (HBV) DNA, or positive hepatitis C virus (HCV) antibody (confirmed with presence of HCV RNA if needed) at screening.
	E 16.	At baseline, presence of any conditions listed as criteria for IMP discontinuation (see Section 10.3)
	E 17.	Presence of skin comorbidities that may interfere with study assessments
	E 18.	History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin

	E 19. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization E 20. History of alcohol or drug abuse within 2 years of the screening visit E 21. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to, patients with short life expectancy, patients with uncontrolled diabetes (Glycated hemoglobin [HbA1C] ≥9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepatobiliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, and rheumatoid arthritis), and other severe endocrinological, gastrointestinal, metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc) E 22. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the Investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRFs, etc) E 23. Planned or anticipated major surgical procedure during the patient's participation in this study E 24. Patient is a member of the investigational team or his/her immediate family E 25. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study E 26. Woman of childbearing potential (WOCBP) not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy (see contraceptive guidance in Appendix A)
Total expected number of patients	160 patients
STUDY TREATMENTS	
Investigational medicinal products **Formulation** **Route of administration** **Dose regimen**	Dupilumab or matching placebo Dupilumab: 150 mg/mL in a prefilled glass syringe to deliver 300 mg in 2 mL; Placebo: prefilled syringe to deliver 2 mL Subcutaneous Patients will be randomized 1:1 to the following regimen from Week 0 through Week 14: • Dupilumab 300 mg SC q2w following a 600 mg (ie, two 300 mg SC injections) loading dose • Placebo SC q2w in prefilled syringe to deliver 2 mL following a placebo loading dose

Noninvestigational medicinal product	**Background treatment** Moisturizers (emollients) **Rescue treatment** If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD is allowed (see Section 8.2.2).
Formulation	Moisturizers (emollients): topical formulation Rescue treatment: referring to label
Route of administration	Moisturizers (emollients): topical use Rescue treatment: referring to label
Dose regimen	Moisturizers (emollients): twice daily for at least 7 days before randomization and to continue the treatment throughout the study. Rescue treatment: referring to label
ENDPOINTS	**Primary endpoint** 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 **Secondary endpoints** **Efficacy:** • Proportion of patients with EASI-75 response (reduction of EASI score by ≥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 Dermatology Life Quality Index (DLQI) • Change from baseline to Week 16 in Patient Oriented Eczema Measure (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 EuroQol five dimensions questionnaire (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

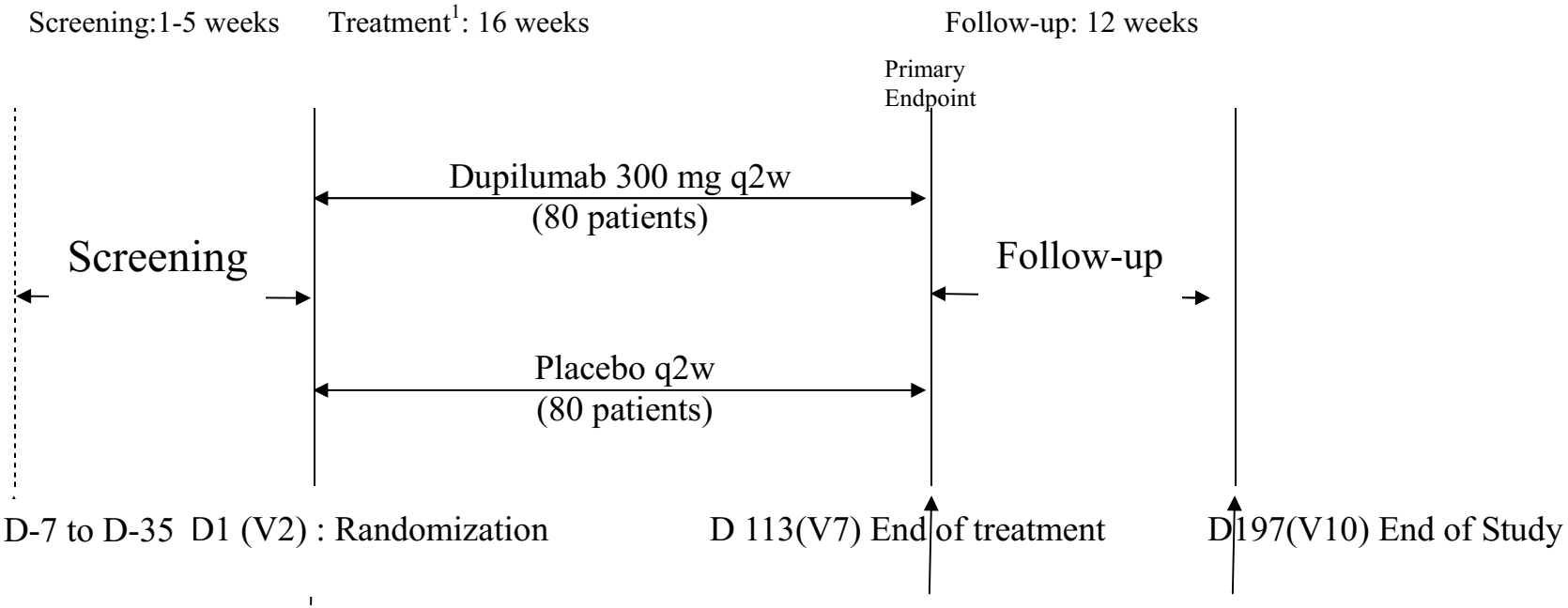
	• Absolute and percent changes in weekly average of peak daily pruritus NRS score from baseline through Week 16 • The proportion of patients who responded "absence of pruritus" or "mild pruritus" in the pruritus categorical scale at Week 16 • Number of days and proportion of patients with sick leave/missed school days **Safety:** Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of specific interest (AESIs), clinical laboratory evaluations, vital signs, physical examination, weight and height, electrocardiogram (ECG). Immunogenicity.
ASSESSMENT SCHEDULE	Screening period: 7-35 days Randomized treatment period: 16 weeks Post-treatment period: 12 weeks
STATISTICAL CONSIDERATIONS	**Sample size determination:** 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. **Analysis population:** The intent-to-treat (ITT) population includes all randomized patients. Efficacy analysis will be based on treatment allocated at randomization (as randomized). 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 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 The safety population includes all randomized patients who received any IMP; it is based on the treatment patients actually received (as treated). **Primary analysis:** The Cochran-Mantel-Haenszel test adjusted by baseline disease severity (moderate or severe) will be used for the percentage of patients with IGA 0 or 1 and a reduction from baseline of ≥2 points at Week 16 on the ITT population. If rescue medication or procedure is used, the patient will be specified as a non-responder from the time the rescue is used. If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal.

	Analysis of secondary endpoints: For binary endpoints, the secondary efficacy analysis will use the same approach as that used for the primary analysis. To account for the impact of rescue medication or procedure on the efficacy effect: for 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 continuous efficacy endpoints will be analyzed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model with treatment, randomization strata (disease severity), and relevant baseline value included in the model as the primary analysis. Patient's efficacy data after rescue medication up to Week 16 will be set to missing and then imputed by the MI method. Safety Analysis: Will be based on the safety population.This includes TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and ECG results). A summary of safety results for each treatment group will be presented. Anti-drug antibody results will be presented.
DURATION OF STUDY PERIOD (per patient)	28 weeks, including 16-week treatment period and 12-week follow-up. The total study duration will be up to 33 weeks.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

Figure 1 - Graphical Study Design



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.

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.

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]

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AD:	atopic dermatitis
ADA:	anti-drug antibody
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANA:	anti-nuclear antibody
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BSA:	body surface area
CFDA:	China Food and Drug Administration
CPK:	creatine phosphokinase
CRF:	case report form
CV:	curriculum vitae
CYP:	cytochrome P450
DLQI:	dermatology life quality index
DRF:	discrepancy resolution form
EASI:	eczema area and severity index
ECG:	electrocardiogram
eCRF:	electronic case report form
EQ-5D:	EuroQol five dimensions questionnaire
EQVAS:	EQ visual analogue scale
FSH:	follicle stimulating hormone
GCP:	good clinical practice
GSO:	Global Safety Officer
HbA1C:	glycated hemoglobin
HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
HRT:	hormonal replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IFN-γ:	interferon-gamma
IGA:	Investigator's Global Assessment
IgE:	immunoglobulin E
IL:	interleukin

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

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

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 (4, 5, 6). Biological agents, including anti-tumor necrosis factor (TNF) α (infliximab and etanercept), anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti-CD11a (efalizumab), have generally been ineffective in clinical trials (7, 8, 9). Therefore, there exists a significant unmet medical need for an alternative treatment for AD.

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

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 subjects 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.

4.2 RATIONALE

4.2.1 Rationale for Study Design

This study has been designed as 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 (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.

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]

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.

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

and are potentially eligible for treatment with dupilumab after appropriate washout, subject to approval by the sponsor.

- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the Investigator or by the patient's treating physician.
- Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician. If documentation is inadequate, potential patients may be re-screened after such documentation is obtained (ie, patients are shown to fail a 28-day course of mid-to-higher potency TCS [±TCI]).

I 08. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (NOTE: See E 07 for limitations regarding emollients) (See background treatment with topical emollient in Section 8.2)

I 09. Willing and able to comply with all clinic visits and study-related procedures

I 10. Able to understand and complete study-related questionnaires

I 11. Signed written informed consent

7.2 EXCLUSION CRITERIA

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

E 01. Participation in a prior dupilumab clinical study

E 02. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit

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 is longer
- 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 Section 8.8.1) and procedures during study treatment

E 10. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit

E 11. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals,antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit
NOTE: patients may be rescreened after infection resolves

E 12. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or unusually frequent, recurrent, or prolonged infections, per Investigator's judgment

E 13. Active TB, latent untreated TB, or a history of potentially incompletely treated TB or non-TB mycobacterial infection, unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing would be performed according to local guidelines if required by regulatory authorities or ethics commitees

E 14. History of HIV infection or positive HIV serology at screening

E 15. Active hepatitis or patients with positive HBsAg, or patients with positive HBcAb plus positive HBV DNA, or positive HCV antibody (confirmed with presence of HCV RNA if needed) at screening

E 16. At baseline, presence of any conditions listed as criteria for IMP discontinuation (see Section 10.3)

E 17. Presence of skin comorbidities that may interfere with study assessments

E 18. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin

E 19. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization

E 20. History of alcohol or drug abuse within 2 years of the screening visit

E 21. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to,patients with short life expectancy, patients with uncontrolled diabetes (HbA1c ≥9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepatobiliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, and rheumatoid arthritis), and other severe endocrinological, gastrointestinal,metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRFs, etc)

E 22. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the Investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRFs, etc)

E 23. Planned or anticipated major surgical procedure during the patient's participation in this study

E 24. Patient is a member of the investigational team or his/her immediate family

E 25. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study

E 26. Woman of childbearing potential (WOCBP) not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy (see contraceptive guidance in Appendix A)

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

8.1.1 Dupilumab

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

8.1.2 Placebo

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

8.1.3 Dosing schedule

Patients will receive q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg (ie, two 300 mg SC injections) on Day 1, or q2w injections of matching placebo (following a placebo "loading dose") during the 16-week treatment period. Subsequently q2w SC injections after loading dose of IMP will be given every 14 ± 3 days (q2w). The doses of the IMP must be separated by ≥11 days. Patients will be monitored at the study site for a minimum of 30 minutes after the injection of the IMP for any signs or symptoms of a hypersensitivity reaction. Patients will have the option to 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). The study staff will train the patient/caregiver on preparation and administration of the IMP on Day 1 and will administer the first of the 2 injections required for the loading dose. The patient/caregiver will administer the second injection required for the loading dose under the supervision of the clinic staff. The patient/caregiver will administer the IMP under the supervision of the clinic staff at Visits 3 and 4 (Weeks 2 and 4, respectively). Patients who prefer to have the clinic staff administer the IMP may choose to have injections administered in the clinic.

The procedure for preparing the dupilumab dose for SC injection will be provided in the pharmacy manual. Subcutaneous injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms, so that the same site is not injected twice consecutively. To allow for adequate assessment of possible injection site reactions (ISRs), the IMP should be administered only into areas of normal-looking skin. Instructions for recording and reporting ISRs will be provided in the user guidance.

8.1.4 Dose modification and investigational medicinal product discontinuation rules

8.1.4.1 Drug modification

Dose modification for an individual patient is not allowed.

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.

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.

A randomized treatment kit number list will be generated centrally by the sponsor. The IMP (dupilumab or placebo) will be packaged in accordance with this list.

The sponsor will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system. This centralized treatment allocation system will generate the patient randomization list, according to which it will allocate the treatments to the patients.

Patients may be rescreened once if they fail the screening evaluation for reasons related to incidental transitory conditions. A different patient identification will be issued. There is no requirement for a waiting period between the screen-failure date and the rescreening date. The IRT report will flag rescreened patients. Patients that are rescreened must sign a new consent form and all Visit 1 procedures must be repeated.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file.
A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Dupilumab and placebo will be supplied as one glass prefilled syringe packed in a patient kit box. Both the glass prefilled syringe and the box will be labeled. Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

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

8.6 STORAGE CONDITIONS

Investigational medicinal products will be stored at the site at a temperature of 2°C to 8°C in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, policies and procedures. Control of the IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the compound should be managed according to the rules provided by the sponsor.

The IMP will be shipped at a temperature of 2°C to 8°C to the Investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened IMP will be destroyed or returned to the sponsor or designee.

8.7 RESPONSIBLILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply the IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose the IMP in any other manner.

8.7.1 Treatment accountability and compliance

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP dispensed, used, and returned by each patient. The IMP dispensation/accountability log is to be updated each time the IMP is dispensed or returned. Any IMP not returned (even if considered empty) must be accounted for with a comment in the log. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to verify accountability.

All drug accountability records must be kept current.

The Investigator must be able to account for all opened and unopened IMPs. These records should contain the dates, quantity, and IMP

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

Patients will be instructed to return their used and unused IMP to the investigation site. Compliance with IMP administration will be reviewed with the patient at each visit. Compliance will be assessed by inspection of the kit box and checking the unused glass pre-filled syringe.

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

8.7.2 Return and/or destruction of treatments

All used, partially-used or unused treatments will be retrieved by the sponsor or destroyed at study site. All used prefilled syringes should be kept in a sharp container by the patients and be returned to sites for destroy.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the sponsor provides written authorization.

For noninvestigational medicinal product (NIMP) not provided by the sponsor, tracking and reconciliation has to be achieved by the Investigator and need to be captured in standard site documents and records (eg, medical notes).

8.8 CONCOMITANT MEDICATION

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

8.8.1 Prohibited medications and procedures

The following treatments are prohibited during the study:

- Treatment with a live (attenuated) vaccine (See Appendix B)
- 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, TCM, or any other therapeutic agents for AD that were not properly evaluated in clinical trials

However, at the discretion of the Investigator, patients were permitted to receive rescue treatment with some of the otherwise prohibited medications noted below. Rescue treatment (see Section 8.2.2 for details) is only to be performed when medically necessary for worsening AD signs and/or symptoms requiring initiation or escalation of treatment.

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)

If a patient receives treatment with systemic corticosteroids or other 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.

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy except as rescue for AD
- Tanning in a bed/booth

8.8.2 Permitted medications and procedures

Other than the prohibited medications listed in Section 8.8.1, treatment with concomitant medications is permitted during the study. This includes basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications for any duration.

Medications used to treat chronic disease such as diabetes, hypertension, and asthma are also permitted; if there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the sponsor.

Cytochrome P450

Study R668-AD-1433, designed to investigate the potential impact of dupilumab on cytochrome P450 (CYP) enzyme activity, shows no evidence for a clinically meaningful effect of dupilumab on the activity of CYP1A2, CYP3A4, CYP2C19, CYP2C9, or CYP2D6. No specific monitoring of CYP enzymes activities is needed.

8.8.2.1 Prohibited concomitant medications or procedures as rescue

If medically necessary (eg, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the Investigator (see Section 8.2.2 for details).

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

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

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

9.1.1 Investigator's global assessment

The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score will be assessed at time points according to Section 1.2.

The IGA is provided in the user guidance.

9.2 SECONDARY ENDPOINTS

9.2.1 Efficacy endpoints

- 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

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.

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

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.

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.

Plots of concentrations of functional dupilumab will be examined and the potential influence of ADA on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics parameters

9.3.1.1 Pharmacokinetic measurements

Samples for measurement of functional dupilumab concentration in serum will be collected at time points listed in Section 1.2.

9.3.1.2 Pharmacokinetic parameters

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

- C_{trough} over time

[redacted]

[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)

- 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

- All questionnaires will be administered before any invasive procedures:
  - POEM
  - DLQI
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- BSA
- Laboratory testing:
  - Urine pregnancy test (WOCBP only)
- 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
- Dispense the patient dosing diary and the IMP for Week 6 if the patient chooses to self-inject at home at Week 6.

10.1.2.4 Visit 5/ Week 8/Day 57 (±3 days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- If the patient chose to self-inject the IMP on Week 6, review the patient dosing diary and account for the IMP. Collect any unused IMP.

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
- Laboratory testing:
  - Hematology and chemistry
  - Urine pregnancy test (WOCBP only)

- Administer the IMP after all the other assessments have been performed. Train patient/caregiver in injection technique (if needed) 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
- Dispense the patient dosing diary and the IMP for Week 10 if the patient chooses to self-inject at home at Week 10.

10.1.2.5 Visit 6/Week 12/Day 85 (±3 days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- If the patient chose to self-inject the IMP on Week 10, review the patient dosing diary and account for the IMP. Collect any unused IMP.

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
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- BSA
- Laboratory testing:
  - Urine pregnancy test (WOCBP only)
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample
- Administer the IMP after all the other assessments have been performed. Train patient/caregiver in injection technique (if needed) 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
- Dispense the patient dosing diary and the IMP for Week 14 if the patient chooses to self-inject at home at Week 14.

10.1.2.6 Visit 7/End of Treatment/Week 16/Day 113 (±3 days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- If the patient chose to self-inject the IMP on Week 14, review the patient dosing diary and account for the IMP. Collect any unused IMP.

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
- Physical examination
- ECG
- Laboratory testing:
  - Hematology and chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - [redacted]
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample

10.1.3 Follow-up Period

10.1.3.1 Visit 8/Week 20/Day 141 (±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
- POEM
- DLQI
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- BSA

10.1.3.2 Visit 9/Week 24/Day 169 (±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
- POEM
- DLQI
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- BSA

10.1.4 Visit 10/End of Study Visit/Week 28/Day 197 (±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
- POEM
- DLQI
- EQ-5D
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI

- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology and chemistry
  - Urinalysis
  - Serum pregnancy test (WOCBP only)
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample

10.1.5 Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (Week 16) will be asked to return to the clinic for 2 visits: once for early termination assessments, and again at Week 16 (primary endpoint visit), as described in Section 10.1.2.6. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments.

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS and pruritus categorical scale
- POEM
- DLQI
- EQ-5D
- Assess sick leave/missed school days
- Vital signs
- IGA
- EASI
- BSA
- Photograph AD area (select sites only)
- Weight
- Physical examination
- ECG
- Laboratory testing:
  - Hematology and chemistry

- Urinalysis
- Serum pregnancy test (WOCBP only)
- [redacted]
- Functional dupilumab PK sample
- Anti-dupilumab antibody sample

10.1.6 Unscheduled Visits

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

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Pruritus NRS and pruritus categorical scale
- POEM
- DLQI
- 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)
  - [redacted]
  - Functional dupilumab PK sample
  - Anti-dupilumab antibody sample

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.

10.3.2 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.

Patients who permanently discontinue the IMP will be asked and encouraged to return to the clinic for study visits and participate in assessments according to the visit schedule until the end of the study with a ± 3 day window (see Section 10.1.5). Under exceptional circumstances when a patient cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and concomitant medication should be collected.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records checks. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any adverse event information elicited should be documented.

Patients may withdraw consent verbally or in writing and, if verbal, then the site needs to document in source records that patient withdrew consent verbally.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a systemic drug concentration sample, if appropriate, and 3 posttreatment follow-up period visits.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contacts, and receipt for sending a registered letter).

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

Patients prematurely discontinued from the study will not be replaced.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Anaphylaxis (refer to Appendix C for definition of Anaphylaxis)
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse
  - ALT >3 ULN + total bilirubin >2 ULN or ALT increase >10 ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Cancers diagnosed during the study or aggravated during the study
  - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

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.

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

laboratory testing at Visit 1 adds hepatitis screen (HBsAg, HBsAb, HBcAb [HBV DNA will be tested for patients who present with HBsAg negative and HBcAb positive at screening and may be performed prior to randomization], and HCV Ab [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]). Active hepatitis or patients with positive HBsAg, or patients with positive HBcAb plus positive HBV DNA, or positive HCV Ab (confirmed with presence of HCV RNA if needed) at Visit 1 are excluded from the study.

Guidance for the investigation of elevated ALT as well as concurrent management of IMP is provided in Appendix E.

10.6.5 Ocular surface disease

Patients with signs of any ocular surface disease, eg, conjunctivitis and blepharitis, will be referred to an ophthalmologist. Any baseline findings will be documented as part of the patient's medical history and/or physical exam, as appropriate.

Any inflammatory ophthalmological condition that occurs post-baseline will be captured as an AE. Patients with any ocular surface diseases post-baseline (even lasting for less than 4 weeks) should be referred to an ophthalmologist for further evaluation and treatment.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

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).

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.

11.4.2 Extent of study treatment exposure and compliance

11.4.2.1 Extent of investigational medicinal product exposure

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 number (%) of patients randomized and exposed to double-blind IMP will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, standard deviation, minimums, medians, and maximums.

A summary of the number of doses by treatment group will be provided.

11.4.2.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data. The compliance with 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%.

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

11.4.3 Analyses of efficacy endpoints

11.4.3.1 Analysis of primary efficacy endpoint

Primary Hypotheses:

The following hypotheses will be tested:

H0: No treatment difference between dupilumab and placebo

H1: There is a treatment difference between dupilumab and placebo

Primary analysis

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 on the ITT population. The analysis of primary endpoint on the PP population will be supportive.

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.

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.

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.

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.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATORS

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

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

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

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the preidentified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the sponsor to record (according to sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the IB and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party’s account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the sponsor or its designee are and remain the sole property of the sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the sponsor.

The sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the sponsor, at the sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

The patient's personal data, which are included in the sponsor database, shall be treated in compliance with all applicable laws and regulations;

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the sponsor's databases, shall be treated by both the sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race and ethnicity will be collected in this study because these data are required by the regulatory authority (ie, on Chinese population for the China Food and Drug Administration [CFDA]).

The data collected in this study will only be used for the purposes of the study and to document the evaluation of the benefit/risk ratio, efficacy and safety of the product. They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not relieve the Investigator and the collaborators from any

obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

Financing and insurance information is provided as a separate agreement.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the sponsor and authorize the sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the sponsor.

The Investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the sponsor

The sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected.

In any case the sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the sponsor's written consent, being understood that the sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the sponsor. The sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be recollected if necessary.

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy.
2. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
  - Refrain from donating sperm

    and
  - At least 1 of the following conditions applies:
    - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

      or
    - Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects)
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] - oral - injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*)

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 12 weeks after the last dose of study treatment.

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationb - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] - oral - injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 12 weeks after the last dose of study treatment.

Appendix B List of Prohibited Live, Attenuated Vaccines

Bacillus Calmette-Guérin (BCG) anti-tuberculosis vaccine

Chickenpox (Varicella)

Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted

Measles (Rubeola)

Measles-mumps-rubella (MMR) combination

Measles-mumps-rubella-varicella (MMRV) combination

Mumps

Oral polio (Sabin)

Oral typhoid

Rotavirus

Rubella

Smallpox (Vaccinia)

Varicella Zoster (shingles)

Yellow fever

Appendix C Definition of Anaphylaxis

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."

(Adapted from Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117: 391-397)

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a <u>likely</u> allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch0flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *<u>known</u> allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[a]
   b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

Abbreviations: PEF: peak expiratory flow; BP: blood pressure.

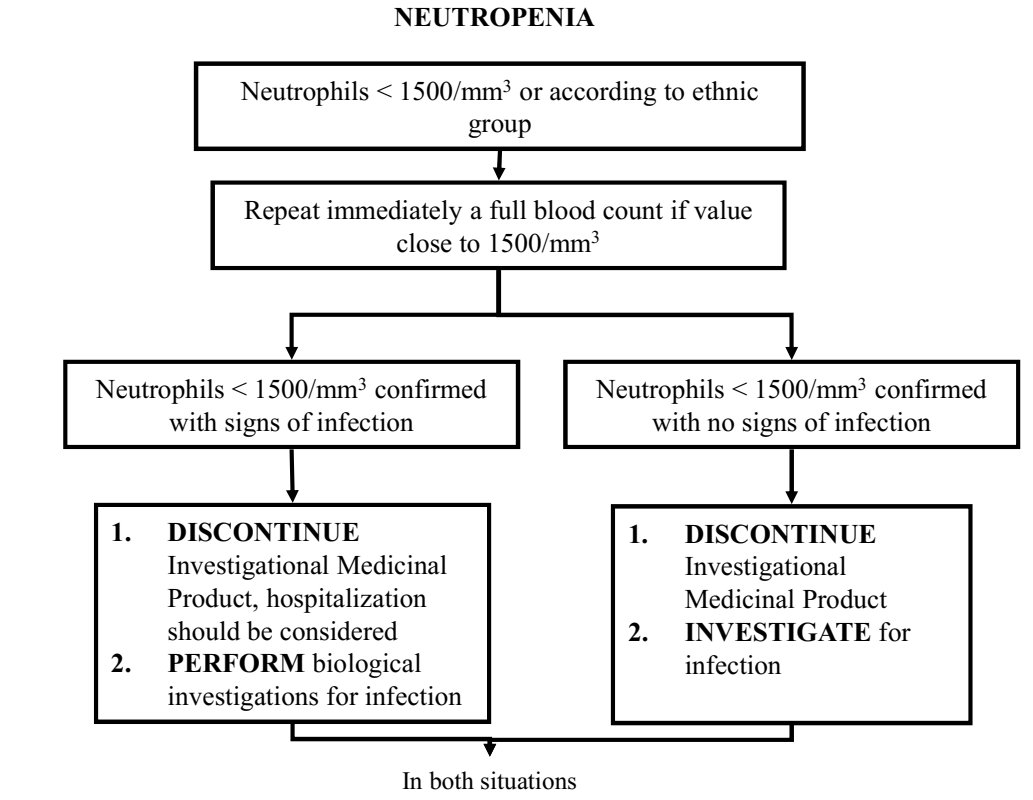
a Low systolic pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 * age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Appendix D Opportunistic infection

The list below is indicative and not exhaustive:

- Aspergillosis
- Blastomyces dermatitidis
- Candidiasis – only systemic or extensive mucosal or cutaneous cases.
- Coccidioides immitis
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (disseminated)
- Herpes Zoster (disseminated; ophthalmic; involvement of 2 or more dermatomes)
- Histoplasmosis (pulmonary or disseminated; most common in tropical areas)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)

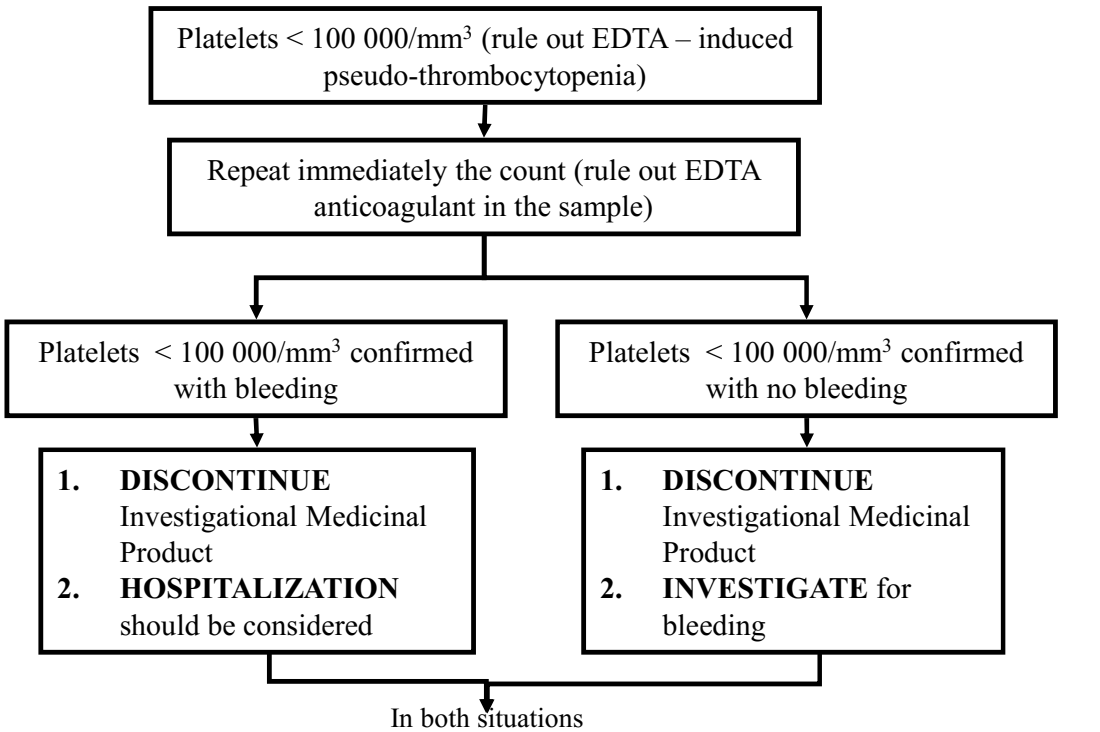
Appendix E General Guidance for the follow-up of laboratory abnormalities by Sanofi



Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

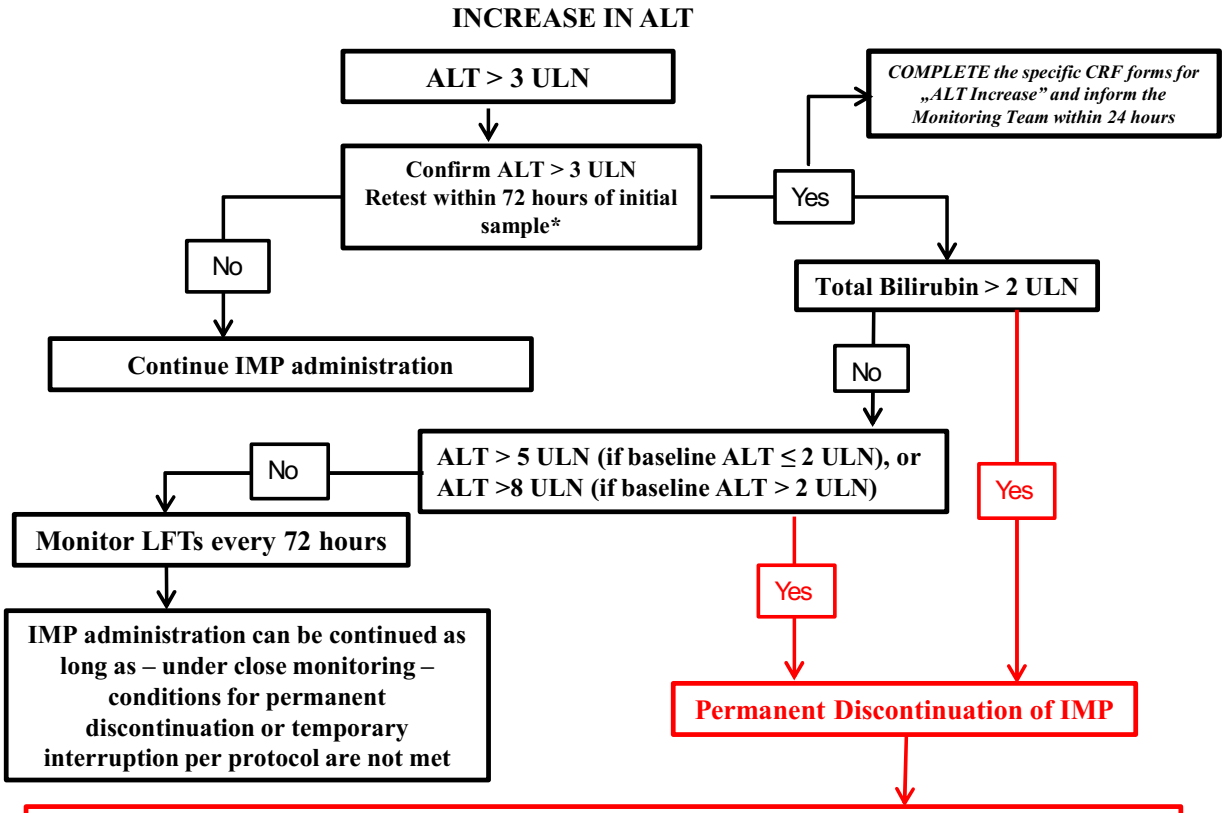
Neutropenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.



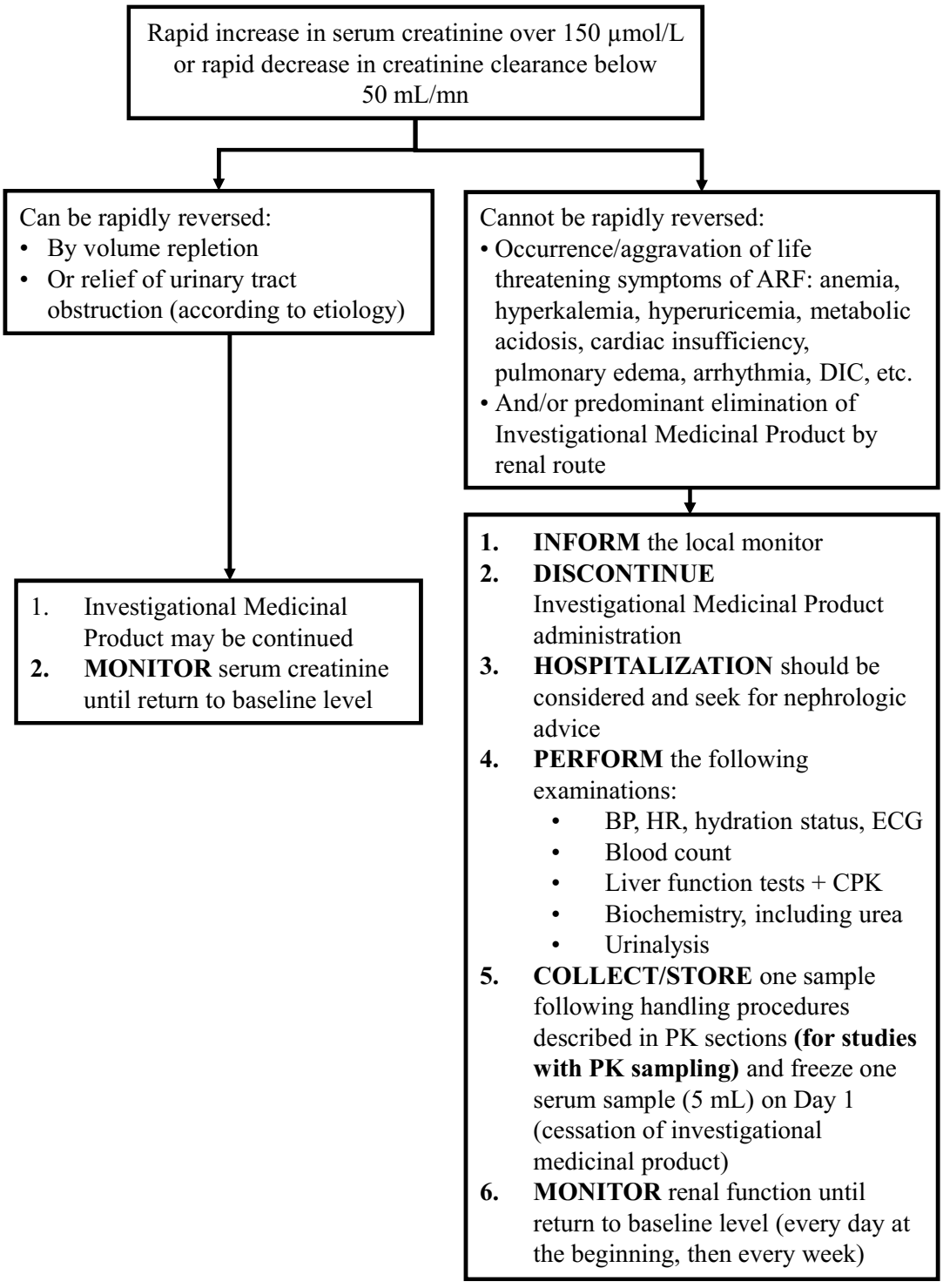
In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - A*s closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:

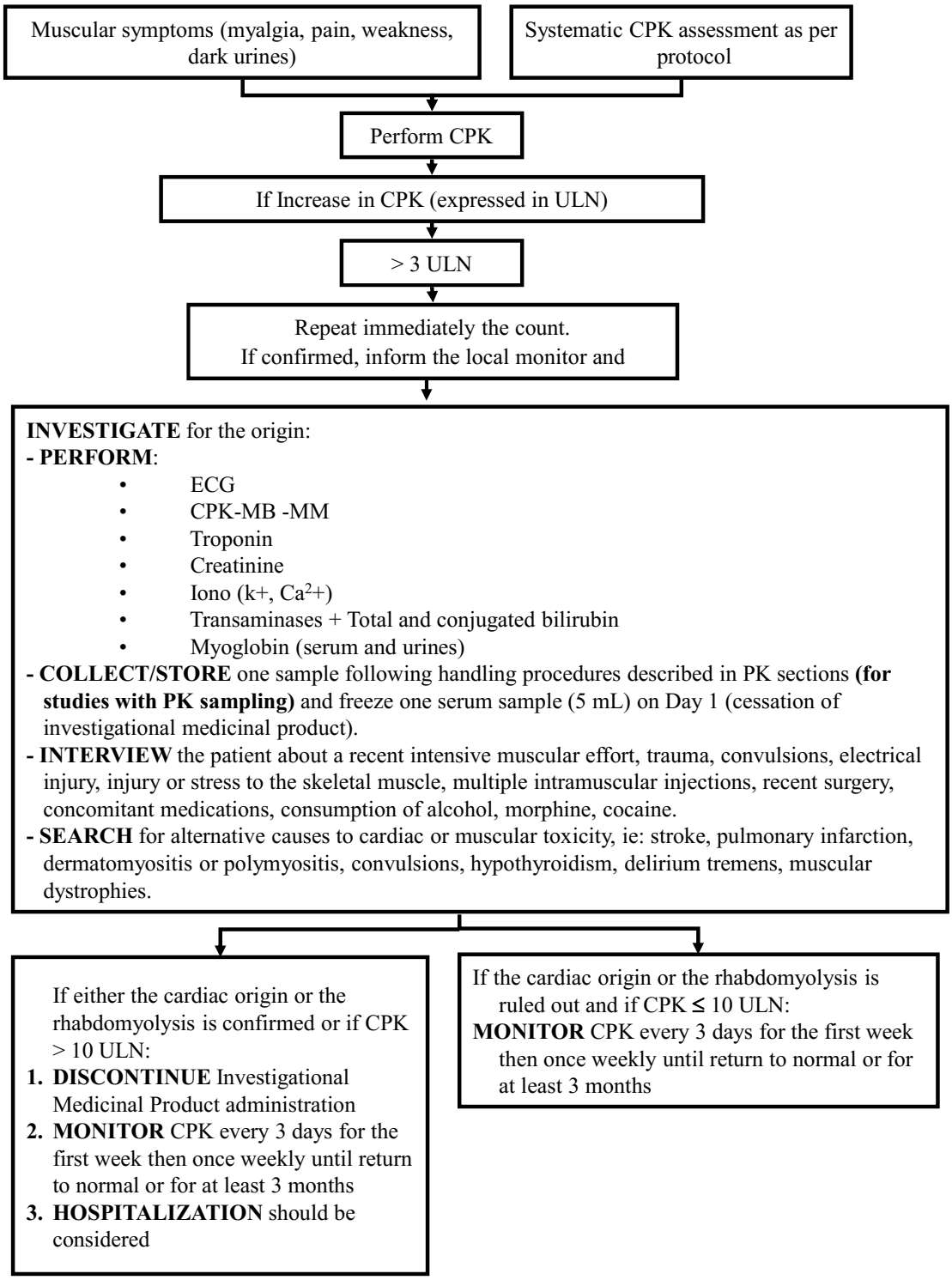
- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.4 for guidance on safety reporting.
- Normalization is defined as ≤ ULN or baseline value, if baseline value is >ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria in the General guidelines for reporting adverse events in Section 10.4.2 is met.