AMENDED CLINICAL TRIAL PROTOCOL 01

NCT04823130

Protocol title:	**A multi-center, exploratory study to assess dupilumab effect on pruritus neuro-mechanisms in patients with atopic dermatitis**
Protocol number:	**LPS16763**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR231893/REGN668 dupilumab/Dupixent®**
Study phase:	**Phase 4**
Short title:	**DupIlumab eFFEct on pRuritus nEuro-mechaNismS in paTients with Atopic Dermatitis - DIFFEREN-STAD**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	06 January 2021, version 1 (electronic 1.0)
Original Protocol		17 August 2020, version 1 (electronic 1.0)

Amended protocol 01 (06 January 2021)

This amended protocol (Amendment 01) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

This protocol was amended per health authority request in order to remove ankle as a location for skin biopsy.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities (SOA)-AD participants	Deleted “and ankle” from footnote e.	To remove ankle as a location for skin biopsy per health authority request due to potential risk of infection related to this location.
Section 1.1 Synopsis-overall design, Section 4.1 Overall design, Section 8.3 Exploratory assessments and biomarkers	Revised in Section 1.1: Collection of skin biopsies of lesional skin at baseline and post-lesional skin at the end of treatment (EoT) (Week 17) is mandatory for all AD participants. According to patient tolerability to the skin biopsy and at Investigators discretion, additional optional biopsies of post-lesional skin will be collected at Week 3 and Week 21. Revised in Section 4.1: Collection of skin biopsies of lesional skin at baseline and post-lesional skin at the end of treatment (EoT) (Week 17) is mandatory for all AD participants. If possible, a post lesional skin biopsy at Week 3 and Week 21.	To clarify the post-lesional skin biopsies collection schedule and to keep consistent with Section 1.3 as requested by health authority.

Section # and Name	Description of Change	Brief Rationale
	Revised in Section 8.3: Two Skin biopsies will be collected once in healthy participants and repeatedly (at least twice; baseline and Week 17) from lesional and post-lesional skin in AD participants for exploratory assessments and a broad panel of biomarkers. Further biopsies from post-lesional and non-lesional skin are optional for AD participants.	
Section 1.1 Synopsis	Changed "2 to 4 weeks" to "up to 4 weeks" • Screening Period: up to 4 weeks before inclusion. Changed "21 weeks" to "20 weeks" • Total duration of Observation Period: up to 20 weeks.	To keep consistent with the schedules in Section 1.3.
Section 1.2 SCHEMA	Changed Week 2 to Week 3, Week 16 to Week 17, and Week 20 to Week 21 in the graphical study design. Changed "N=40" to "34 AD participants".	To keep consistent with the schedules in Section 1.3 and study population in Section 5.
Section 1.3 Schedule of activities (SOA)-AD participants	Added an annotation g to Non-lesional skin sample collection at baseline to indicate this biopsy is optional.	To keep consistent with the skin biopsy sample collection procedures in Section 8.3.1.
Section 1.3 Schedule of activities (SOA)-AD participants	Removed IMP dispense from Visit 5.	To correct a discrepancy, no IMP dispense is planned at EOT visit
Section 1.3 Schedule of activities (SOA)-AD participants	Added a footnote j to archival blood sample collection: Whole blood sample collected at baseline and stored during the study for potential analysis if deemed necessary for safety reasons. Will be described in study reference manual. The subsequent footnote numbers were updated accordingly.	To clarify the purpose of the archival blood sample collection
Section 1.3 Schedule of activities (SOA)-AD participants and Section 8.4.2 Vital signs	Removed pulse rate from Section 1.3 and removed both pulse rate and respiratory rate from vital sign parameters in Section 8.4.2.	To correct a discrepancy, heart rate is already part of vital signs, and respiratory rate is not planned/relevant for this study
Section 4.1 overall design	Change 28 days to 21 days: Healthy participants will undergo a Screening Period of 21 days and a 7 days Observational Period following collection of the skin biopsy.	To keep consistency with Section 1.4

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Study intervention(s) administered	Revised from "Week 2 to Week 16" to "Week 3 to Week 15": - Dose regimen: Participants will receive a SC loading dose of dupilumab 600 mg on Day 1, followed by Q2W SC dosing of dupilumab 300 mg (2 mL of a 150 mg/mL solution) from Week 3 to Week 15	To keep consistency with Section 1.3
Section 7.1.2 Temporary discontinuation	Removed "and rechallenge" from the section title, and added: Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (eg, natural disaster, pandemic, etc) (see Section 6.1). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF. Temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the participant.	To reflect the update in the protocol template regarding regional or national emergency declared.
Section 8.1 Efficacy assessments	Removed "screening or" from the following sentence: Patient reported outcomes will be collected in an appropriate form, for which the respective device, diary and/or instruction is handed out to the patient at the Screening (or Baseline) Visit.	To keep consistent with the schedule of activities described in Section 1.3.
Section 8.2 Standardized photographs	Added: photography will be done for healthy participants on Day 1.	To keep consistent with the schedule of activities described in Section 1.4.
Section 8.3.1 Skin Biopsy Samples	Revised the temperature from -80°C to -70°C: A) Fixation with paraformaldehyde (PFA) and freeze at -70°C B) Transfer into RNAlater solution and store at -70°C	To reflect the change from laboratory.
Section 8.5.4 Regulatory reporting requirements for SAEs	Revised "adverse events" to "serious adverse events": Serious adverse events that are considered expected will be specified in the reference safety information (IB). Revised the SUSARs reporting process to: Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.	To reflect the change in the latest protocol template

Section # and Name	Description of Change	Brief Rationale
Section 9.4.8.1.1 Definitions	Removed: Their severity will be graded according National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.	To correct a discrepancy: the criteria are not applicable for this study
Section 9.4.8.2 Vital signs	Revised: For AD participants, heart rate, systolic and diastolic blood pressures (SBP and DBP), and body temperature will be analyzed as raw parameter value and change from baseline. Body weight will be analyzed as raw parameter value.	To keep consistent with the schedule of activities described in Section 1.3.
Section 10.2 Appendix 2: Clinical laboratory tests	Removed: Alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)]. Removed “or specify other tests” from the following sentence: Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests). Removed: The results of each test must be entered into the eCRF.	To keep consistent with the schedule of activities described in Section 1.3.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints, and Section 9.4.7 Description of efficacy variables	Revised “change” or “outcome” from singular to plural in several items.	Editorial changes.
APPENDIX 8: Protocol amendment history	Added: APPENDIX 8: PROTOCOL AMENDMENT HISTORY The Protocol Amendment Summary of Changes Table for the current amendment is located before the Table of Contents (TOC).	To follow the amended protocol process

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A multi-center, exploratory study to assess dupilumab effect on pruritus neuro-mechanisms in patients with atopic dermatitis

Short title: DupIlumab eFFEct on pRuritus nEuro-mechaNismS in paTients with Atopic Dermatitis - DIFFEREN-STAD

Rationale:

Chronic itch is a defining symptom of atopic dermatitis (AD). Inadequately controlled itch is a major burden for AD participants and significantly affects their quality of life (QoL). The basic mechanism behind itch in AD is not fully understood, but crosstalk between the nervous system, the cutaneous immune system, and keratinocyte populations is central to the development and persistence of atopic itch (1). It was also shown that epidermal nerves are aberrantly activated by overexposure to environmental stimuli during the development of AD due to the impaired protection by the epidermal barrier (2). There is a high medical unmet need to better understand the dysregulations of neuromechanistic pathways in AD participants with chronic itch and potential effect of treatments on restoration of the neuronal architecture and inflammation.

The nature of inflammatory pathways in AD is evidenced by the potent therapeutic effects of the interleukin(IL)-4 receptor alpha (IL-4Ra) antagonist dupilumab (1) and other cytokines such as IL-13 and IL-31. While dupilumab has been investigated clinically in several Type 2 immune diseases, including asthma and AD, having shown beneficial impact on itch reduction in Phase 3 clinical trials in both adult and pediatric AD patients, the underlying itch reduction mechanism in AD remains to be elucidated. This exploratory study will assess the effect of dupilumab on both chronic pruritus and peripheral neuronal normalization in AD participants. The study will contribute to the understanding of the neuromechanistic pathways of itch by evaluating pruritus effect on neuronal architecture and neuromarkers. Furthermore, this study will help address a key knowledge gap by generating data to allow the formulation of specific hypotheses concerning the role of the nervous system in underlying the clinical effects of dupilumab.

The findings from this study will provide guidance in designing a larger dupilumab clinical study to assess the benefits of targeting IL-4 and IL-13 on pruritus neuro-mechanisms.

Objectives and endpoints

Objectives	Endpoints
Primary	
• Assess change in neuronal architecture following long term treatment with dupilumab in skin biopsies from AD participants with chronic pruritus	• Change from baseline on Week 17 for intraepidermal nerve fiber density by protein gene product 9.5 (PGP9.5) antibody staining in lesional skin • Change from baseline on Week 17 for nerve fiber branching by PGP9.5 antibody staining in lesional skin
Secondary	
• Assess change in neuronal architecture following short term treatment with dupilumab and during follow-up in skin biopsies from AD participants with chronic pruritus	• Changes from baseline on Weeks 3 and 21 for intraepidermal nerve fiber density by PGP9.5 antibody staining in lesional skin • Changes from baseline on Weeks 3 and 21 for nerve fiber branching by PGP9.5 antibody staining in lesional skin
• To evaluate the efficacy of dupilumab in AD participants with chronic pruritus	• Changes from baseline over time and at Weeks 17 and 21 for the outcomes of the following assessments/questionnaires: - Peak pruritus assessed by numeric rating scale (NRS) - Eczema and severity index (EASI) - Scoring Atopic Dermatitis (SCORAD) - Patient-Reported Outcomes Measurement Information (PROMIS-itch) - Patient Oriented Eczema Measure (POEM) - Dermatology Life Quality Index (DLQI) - Atopic Dermatitis Control Tool (ADCT) - Sleep quality NRS - Skin Pain NRS - Skin Sensitivity NRS - Skin Burning NRS • Proportion of AD participants reaching pruritus NRS ≥4 point improvement from baseline at Weeks 3, 5, 9, 17, and 21
• To evaluate the safety of dupilumab in adult participants with moderate-to-severe AD	• Incidence of treatment-emergent adverse events during the treatment and follow-up period

Overall design:

- Open-label, multi-center, single-arm, non-controlled, exploratory study.
- Moderate-to-severe AD participants with chronic pruritus (N=34) and healthy participants (up to N=10, will serve as control group providing normal skin reference for baseline skin biopsy derived endpoints; matched for gender, age, race and anatomical site of skin biopsy).

- A 20-week Observation Period including 16 weeks of treatment for AD participants and a 4-week follow-up period.
- Loading dose of 600 mg dupilumab followed by 300 mg every 2 weeks (Q2W).

This is a 20-week, open-label, multi-center, single-arm exploratory study with a 4-week Screening Period, 16-week Treatment Period, and a 4-week post-treatment Follow-up Period designed to investigate the effect of dupilumab on neuronal architecture and neuronal markers in skin biopsies of lesional skin and compare these results with patient-reported outcomes (PRO) and clinical assessments in approximately 34 patients with moderate-to-severe AD. Collection of skin biopsies of lesional skin at baseline and post-lesional skin at the end of treatment (EoT) (Week 17) is mandatory for all AD participants. According to patient tolerability to the skin biopsy and at Investigators discretion, additional optional biopsies of post-lesional skin will be collected at Week 3 and Week 21. Collection of skin biopsies of non-lesional skin from AD participants at baseline is also optional.

Skin biopsies taken from healthy skin from healthy donors will serve as control.

Disclosure statement:

This is an interventional, exploratory, single-arm study where the primary purpose is advancing science (evaluate dupilumab effects on neuronal architecture and neuromarkers) in AD participants with a single dupilumab treatment arm and a treatment free control group of healthy participants.

Number of participants:

A total of 34 AD participant will be enrolled (and treated with dupilumab) and up to 10 healthy participants will be enrolled following completion of AD patient enrolment to serve as a control group for skin biopsy derived endpoints at baseline.

Intervention groups and duration:

Study intervention(s) in AD participants and duration

Patients with AD who meet the inclusion and exclusion criteria will be part of the following investigational medicinal product (IMP) treatment group with the following periods:

- Screening Period: up to 4 weeks before inclusion.
- Treatment Period: 16 weeks after inclusion including open-label dupilumab treatment starting with a 600 mg loading dose followed by 300 mg Q2W.
- Follow-up Period: 4 weeks following EoT.
- Total duration of Observation Period: up to 20 weeks.
- Total study duration per participant: 22 to 25 weeks.

Healthy Participants

- Screening Period: 1 to 3 weeks before inclusion.
- Observation Period: 7 days after inclusion and collection of skin biopsy.
- Total study duration per participant: 2 to 4 weeks.

Healthy participants will not receive any IMP treatment.

Investigational medicinal product

Dupilumab 300 mg:

- Formulation: Dupilumab 300 mg: A 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in a 2 mL injection.
- Route of administration: Subcutaneous (SC) injection.
- Dose regimen: 300 mg Q2W after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1.
- No dose adjustments allowed.

Statistical considerations:

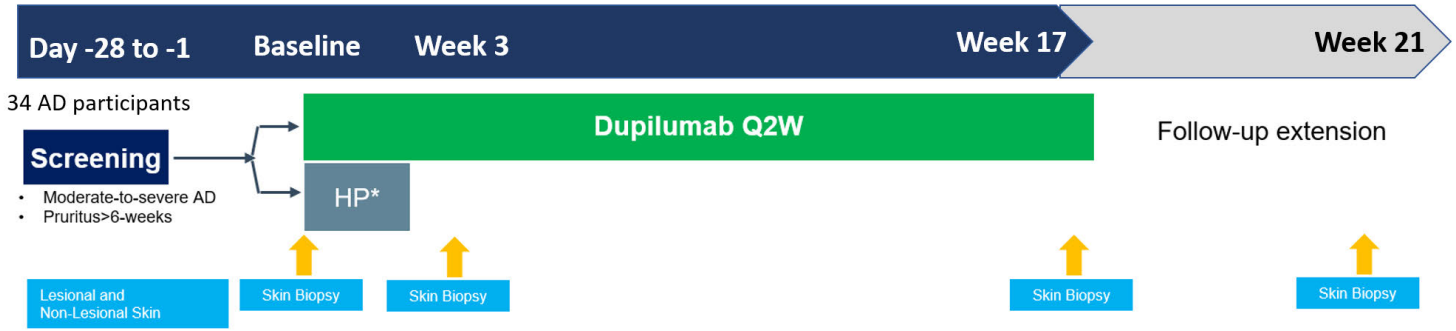
- **Sample size calculation**
  - Sample size for this exploratory study was based on medical/clinical judgment and is consistent with the sample size from similar studies. No formal sample size calculation was performed. Drop-outs will not be replaced.
- **Analysis of primary, secondary, and exploratory endpoints**
  - This is an exploratory study. No formal statistical testing will be conducted.
  - Descriptive statistics will be generated by group and time point for selected parameters of interest. Raw data and changes from baseline (absolute and percent changes) for selected parameters will be summarized in descriptive statistics and summary plots.

Data Monitoring Committee:

Not applicable.

1.2 SCHEMA

Figure 1 - Graphical study design



*Healthy participants will be recruited as control for normal skin biopsy values performed once at baseline.
Abbreviations: AD=Atopic dermatitis; HP=healthy participants; Q2W=every 2 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA) - AD PARTICIPANTS

Phase	Screening	Treatment period										Follow-up	
Day	**D-28 to D-1**	**D1**	**D8**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D113**	**D141**	**D197**
Week	**W-4 to W0**	**W1**	**W2**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17 (EoT)**	**W21 (EoS)**	**W29**
Visit	**1**	**2[a]**		**3**		**4**					**5[b]**	**6**	
Informed consent	X												
Visit at clinical site	X	X		X		X					X	X	
Telephone call													X
Inclusion/exclusion criteria	X	X											
Demographics	X												
Medical/surgical history	X												
Prior/concomitant medications	<----------X---------->												
eDiary[c]		<----------X---------->											
Training for IMP administration and PRO assessments		X		X									
Blood sample[d]		X[a]									X	X	
Skin biopsy[e]													
Pruritic lesional skin		X[a]											
Matched post-lesional healed, non-pruritic non-lesional skin[f]				X[g]							X	X[g]	
Non-lesional skin[g]		X[a,g]											
IMP													
Dupilumab administration[h]		X		X	X[i]	X	X[i]	X[i]	X[i]	X[i]			
IMP dispense		X		X		X							

Phase	Screening	Treatment period										Follow-up	
Day	**D-28 to D-1**	**D1**	**D8**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D113**	**D141**	**D197**
Week	**W-4 to W0**	**W1**	**W2**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17 (EoT)**	**W21 (EoS)**	**W29**
Visit	**1**	**2[a]**		**3**		**4**					**5[b]**	**6**	
IMP accountability and compliance check				X		X					X		
Safety													
Physical examination	X	X[a]										X	
Height		X[a]											
Body weight		X[a]											
Archival blood sample[j]		X[a]											
Serology tests	X												
Vital signs[k]	X	X[a]				X					X	X	
β-HCG test (if applicable)[l]	X	X[a]				X					X	X	
FSH	X												
Adverse event collection	<----------X---------->												
Photography (lesional skin)		X				X					X	X	
Clinician Reported Outcomes (ClinRO)													
IGA	X	X									X	X	
EASI		X		X		X					X	X	
SCORAD		X		X		X					X	X	
Patient-Reported Outcomes (PRO)													
Peak pruritus NRS[m, n]		X	X	X	X	X	X	X	X	X	X	X	
Sleep quality NRS + Skin pain + Sensitivity NRS + Burning NRS[m]		X		X		X		X		X	X	X	

Phase	Screening	Treatment period										Follow-up	
Day	D-28 to D-1	D1	D8	D15	D29	D43	D57	D71	D85	D99	D113	D141	D197
Week	W-4 to W0	W1	W2	W3	W5	W7	W9	W11	W13	W15	W17 (EoT)	W21 (EoS)	W29
Visit	1	2[a]		3		4					5[b]	6	
POEM		X				X		X		X	X	X	
PROMIS-itch		X				X		X		X	X	X	
DLQI		X				X		X		X	X	X	
ADCT		X									X	X	

Abbreviations: ADCT: Atopic Dermatitis Control Tool; ClinRO: Clinician Reported Outcomes; d: day; DLQI: Dermatology Life Quality Index; EASI: Eczema and severity index; eDiary: electronic diary; EoS: end of study; EoT: end of treatment; FSH: Follicle-stimulating hormone; IgE: immunoglobulin E; IGA: Investigator global assessment; IMP: investigational medicinal product; NRS: numeric rating scale; POEM: Patient Oriented Eczema Measure; PRO: patient-reported outcome; PROMIS: Patient-Reported Outcomes Measurement Information; SCORAD: Scoring Atopic Dermatitis; V: visit; w: week; β-HCG: β-Human chorionic gonadotropin.

a All assessments at Baseline Visit (V2) are to be conducted prior to IMP administration.

b Participants who discontinue the study treatment prematurely the end of treatment (EoT) assessments will be performed at the time of discontinuation to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment. In addition, to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study visits and participate in all assessments according to the visit schedule.

c Electronic diary will be dispensed to the patients at Screening Visit (V1) and will be collected on Week 21 (Visit 6). The PROs will be administered to patients via eDiary. Patients will bring the eDiary to the site at each visit, and it will be reviewed and dispensed back to patients at each visit.

d For future use and exploratory research; collection is optional; whole blood sample for DNA extraction will be collected at baseline only.

e Biopsy (4 mm). Skin biopsy in AD participants will be collected in lesional tissue, with acute lesions. Excluding oozing, infections and chronic stages - lichenification. Preferably in the forearms followed by back.

f Post-lesional healed or healing skin should localisation matched to the baseline pruritic lesional biopsy; if post-lesional healed skin that is completely non-pruritic non-lesional is not available at later visits, one of the following biopsies should be collected (in the order of relevance): 1. lesional non-pruritic skin, 2. Post-lesional pruritic skin or 3. lesional pruritic skin

g Optional.

h The IMP will be administered every 14 ±2 days (Q2W) during the 16-week treatment period.

i Self administration by AD patients or caregivers at home.

j Whole blood sample collected at baseline and stored during the study for potential analysis if deemed necessary for safety reasons. Will be described in study reference manual.

k Vital signs, including heart rate, systolic and diastolic blood pressure (mmHg), and body temperature (°C) will be measured.

l Urine pregnancy test could be performed at home with or without the assistance of a home care provider. In case of positive urine test the study treatment will be withheld and a serum pregnancy test should be performed as soon as possible, to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases.

m Participants self assessment.

n To be assessed daily for the first 28 days of treatment, then weekly from Day 29 onwards.

1.4 SCHEDULE OF ACTIVITIES - HEALTHY PARTICIPANTS

Phase	**Screening**	**Observational phase**	**EoS**
Day	**D -21 to D -1**	**D1**	**D8**
Visit	**1**	**2**	**3**
Informed consent	X		
Visit at clinical site	X	X	X
Inclusion/exclusion criteria	X	X	
Demographics	X		
Medical/surgical history, demographics	X		
Prior/concomitant medications	<----------X---------->		
Skin biopsy		X	
Blood sample		X	
Safety			
Physical examination	X		
Height	X		
Body weight	X		
Serology tests	X		
IgE	X		
Adverse event collection	<----------X---------->		
Photography		X	

Abbreviations: D: day; EoS: end of study; V: visit.

2 INTRODUCTION

Dupilumab is a human monoclonal antibody (1) that blocks the shared receptor subunit for IL-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13 cytokines that are key drivers of Type 2 inflammatory diseases (2).

Dupilumab is approved in the United States (US) for the treatment of patients aged ≥6 years with moderate-to-severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable, and for use in adults and adolescents ≥12 with moderate-to-severe AD who are candidates for systemic therapy in the European Union (EU).

2.1 BACKGROUND

Atopic dermatitis is a chronic systemic inflammatory skin disease with a prevalence of up to 25% in children and up to 7% in adults. A large proportion of patients experience sleep disturbance and impaired QoL. Additionally, AD places a heavy economic burden on patients and their family. Atopic dermatitis is caused by the complex interplay between epithelial dysfunction and dysregulated/hyperactivated Type 2 immune response in the skin, with a special role for IL-4/IL-13-driven signaling in AD pathogenesis.

Atopic dermatitis is characterized by disruption of the skin barrier and pruritus (itch), which is the hallmark and most burdensome symptom of AD. Itch profoundly affects patients' daily lives and causes sleep disruption. These negative outcomes are worse with more severe itch. Itch occurs when sensory nerves are exposed to exogenous and endogenous stimuli (pruritogens) including allergens, amines, proteases, neuropeptides, and cytokines. In the peripheral nervous system, the first event is binding of pruritogens to a sub-set of primary afferent C-fiber somatosensory neurons (prurito-ceptors) that innervate skin. Individual pruritoceptors are defined by their signaling response to specific pruritogens (1). One system for functionally classifying groups of pruritoceptors is by sensitivity to histamine, a common pruritogen. Histamine-responsive (histaminergic) and non-histaminergic pruritoceptors use largely distinct receptors and distinct cutaneous nerve fibres that follow separate spinothalamic tracts to connect with different neural pathways in the central nervous system. Activation of many different pruritogen receptors can trigger non-histaminergic pathways relevant to AD. Pruritogens that activate these receptors include keratinocyte-derived proteins, mast cell factors, environmental chemicals, pathogen-derived molecules, and cytokines.

Crosstalk between the nervous system, the cutaneous immune system and keratinocyte populations is central to the development and persistence of atopic itch (1). Additionally, mast cells, eosinophils, and basophils are central effector immune cells in allergic skin inflammation (3). These immune cells interact with other cells in the skin to modulate both innate and adaptive immunity. There is mounting evidence that mast cells, eosinophils and basophils are central to causing pruritus in various skin diseases including AD. These immune cells are considered to be the main source of pruritogens, including histamine, neuropeptides (eg, substance P, calcitonin gene-related peptide [CGRP], vasoactive intestinal peptide [VIP] and pituitary adenylate cyclase-activating polypeptide [PACAP]), interleukins (IL-4, IL-13 and IL-31), cytokines, proteases and lipid mediators and can modulate pruritus through interaction with central and

peripheral nervous systems. T helper cell 2 (Th2) lymphocytes, eosinophils, neutrophils and mast cells amplify inflammatory and pruritoceptive pathways in AD by releasing cytokines and neurogenic peptides. Some AD-associated cytokines, IL-31 and thymic stromal lymphopoietin (TSLP), can directly promote itch via activation of pruritoceptive neurons that express their receptors. In addition, IL-4 may potentiate itch by sensitizing itch-sensory neurons to direct pruritogens, such as histamine and IL-31. Cytokine-to-neuron signaling by IL-31, TSLP and IL-4 - all present in skin during AD flares - may explain the rapid benefit of JAK1/2 and IL-4Rα inhibition versus chronic pruritus and pruritus in AD.

The central nature of inflammatory pathways in AD is also evidenced by the potent therapeutic effects of the IL-4Rα antagonist dupilumab (1). Results from several clinical studies in AD patients have confirmed dupilumab to significantly improve itch in adult and adolescent patients with moderate-to-severe AD (4). Clinical improvements of pruritus in AD patients were observed already after 2 weeks of treatment with dupilumab (1, 5).

2.2 STUDY RATIONALE

Currently there is still a medical unmet need to better understand the dysregulations of neuromechanistic pathways in AD patients with chronic itch and potential effect of treatments on restoration of the neuronal architecture and normalization of itch inducing and pro-inflammatory mediators in the lesional and non-lesional skin. Also, the molecular mechanism by which dupilumab reduces itch sensations in AD patients is not fully understood.

Accordingly, the objective of this exploratory study is to get insights into the effect of dupilumab on both chronic pruritus and peripheral neuronal normalization of AD. The findings from this study will provide guidance in designing a larger dupilumab clinical study to assess the benefits of targeting IL-4 and IL-13 on pruritus neuro-mechanisms.

This study will also contribute to our understanding of the neuromechanistic pathways of itch in AD participants by evaluating the effect of dupilumab on neuronal architecture and neuromarkers and correlating changes with clinical assessment of itch improvement. Furthermore, this study will help addressing a key knowledge gap by generating data to allow formulation of specific hypotheses concerning the role of the nervous system in underlying the clinical effects of dupilumab.

2.3 BENEFIT/RISK ASSESSMENT

Dupilumab has shown clinically relevant benefit in several Type 2 driven immunological disorders, such as AD, bronchial asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP) and eosinophilic esophagitis (EoE). A satisfactory safety profile has been observed so far in completed and currently ongoing studies, including those in AD, nasal polyposis, and asthma patients.

In asthma and AD indications, studies were also conducted in adolescents and similar benefit to adults has been observed. Data showed similar efficacy, safety, and pharmacokinetics (PK) in adult and adolescents.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AE) of dupilumab is available in the Investigator's Brochure (IB) (6).

2.3.1 Risk assessment associated with dupilumab treatment

No tissue targets or specific hazards to humans were identified in nonclinical general and reproductive toxicology studies.

Dupilumab has an extensive safety database. As of 28 March 2020 (Data Lock Point), 10 191 participants were enrolled into the development program for dupilumab and included in the safety population: 382 as healthy participants, 4405 from AD studies, 3614 from asthma studies, 782 from CRSwNP studies, 232 from EoE studies, 248 from the grass allergy, 145 peanut allergy studies, and 511 from the chronic obstructive pulmonary disease (COPD) study, 5 from prurigo nodularis (PN) studies, and 12 from CSU study. The number of participants exposed to dupilumab in clinical studies was 8720 (356 in healthy participants studies, 4052 in AD studies, 3263 in asthma studies, 470 in CRSwNP studies, 166 in EoE studies, 52 in the grass allergy, 96 in peanut allergy studies, and 256 from the COPD studies, 3 from PN studies, and 6 from chronic spontaneous urticaria studies).

Based on the sales figure retrieved from Intercontinental Marketing Services Health and using the World Health Organization's defined daily dose for dupilumab of 21.4 mg/day, the cumulative post marketing exposure to dupilumab is estimated to be 161 582 patient-years (01 January 2017 through 31 March 2020).

Dupilumab was generally well tolerated in all populations tested in clinical development programs consistent with a favorable benefit/risk profile. The adverse drug reactions (ADRs) identified to date for dupilumab include injection site reactions (ISRs), conjunctivitis (including allergic and bacterial), oral herpes, herpes simplex, blepharitis, dry eye, eye pruritus, arthralgia, eosinophilia, and serum sickness. These ADRs were generally mild or moderate, transient, and manageable. These ADRs were not observed consistently in all indications (see IB for greater details [6]). More significant serious allergic reactions were very rare. Importantly, no increased overall infection risk was observed in patients treated with dupilumab.

Systemic hypersensitivity is established as an important identified risk with dupilumab. As protein therapeutics, all monoclonal antibodies are potentially immunogenic. Rare serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD program and anaphylaxis related to dupilumab in the adult asthma clinical trials.

Patients with known helminth infections were excluded from participation in clinical studies; therefore, it is not known if dupilumab will influence the immune response against helminth infections. Consequently, patients with pre-existing helminth infections should be treated for their helminth infection before initiating therapy with dupilumab.

The common ADR across all indications is ISRs. Other potential risks based on the safety profile in particular indications are discussed in the IB (6). It is anticipated that dupilumab in patients with AD will have a favorable safety profile as observed across other Type 2-driven immunological disorders.

2.3.2 Risk assessment associated with other study procedures

Punch skin biopsies of 4 mm diameter will be collected at least twice (baseline and Week 17) in a subset of AD participants and once in healthy participants. Collection of additional skin biopsies at other timepoints (Week 3 and Week 21) and biopsies taken from non-lesional skin are optional for AD participants. Complications are uncommon following this simple procedure but can occur preoperatively, intraoperative, or postoperative (7). Some of the complications associated with punch biopsy include local bleeding and bruising, pain, infection, allergic reaction to the numbing medicine used in the procedure, and damage to the structures beneath the skin site (such as an artery or a nerve). Delayed wound infection is the most common postoperative complication associated with skin biopsy. Later, scarring with or without hypo- or hyperpigmentation is a common complication seen after healing of the skin biopsy site.

2.3.3 Benefit assessment

Dupilumab solution for injection has demonstrated a positive benefit-risk profile and is approved for the treatment of moderate-to-severe AD patients ≥6 years in the US and moderate-to-severe AD patients ≥12 in the EU.

In addition, dupilumab solution for injection is approved for the following indications:

- In the US for use in adults and adolescents (≥12 years) with moderate-to-severe eosinophilic or oral steroid dependent asthma, in the EU for use in adults and adolescents with severe asthma with Type 2 inflammation characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO).
- In the US for use in adults with inadequately controlled CRSwNP and in EU as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Reduction of AD related clinical symptoms including improvement of pruritus have been observed already early after start of dupilumab treatment in the majority of patients included (4). Change in peak pruritus numeric rating scale (NRS) in AD participants was observed as early as 1 to 2 weeks after initiation of dupilumab treatment and was significantly better compared to placebo. Participants with AD disease in this study will receive dupilumab treatment for a total of 16 weeks It is thus expected that patients enrolled in this study will have a clear benefit from being treated with dupilumab; however, there is no final guarantee that the product will help the participant's condition. The participant's skin condition may even get worse by withholding his/her previous/regular AD treatment.

Healthy participants will not benefit directly from participation in this study, other than the nominal reimbursements provided for completing study procedures and visits.

2.3.4 Benefit/risk assessment related to Coronavirus Disease 2019 (COVID-19)

Dupilumab has shown clinical benefit in several type-2 driven immunological disorders, such as AD, asthma, chronic rhinosinusitis with nasal polyposis. In asthma and AD clinical benefit has

also been established in certain pediatric patients (for asthma in adolescents and for AD in 6 to 18-year-old) and a similar benefit-risk profile to adults has been observed.

To date, more than 8000 subjects have been treated with dupilumab during the clinical development program in several indications, of which atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis are licensed in some countries.

Currently, the Sponsor does not have sufficient data in patients with Coronavirus Disease 2019 (COVID-19) and treated with dupilumab. Thus, the safety and efficacy of dupilumab in COVID-19 patients is unknown. During the course of the clinical trial program, respiratory infections including viral infections were monitored and these events are not listed as ADRs with dupilumab.

The target population in this study (LPS16763) is patients with moderate-to-severe AD and healthy participants as reference. Atopic dermatitis, the most common form of eczema, is a chronic inflammatory disease that often appears as a rash on the skin. Moderate-to-severe AD is characterized by rashes that can potentially cover much of the body and can include intense, persistent itching, skin lesions and skin dryness, cracking, redness or darkness, crusting, and oozing. Itch is one of the most burdensome symptoms for patients and can be debilitating.

Based on the aforementioned potential benefits for AD patients treated with dupilumab (Section 2.3.3), the benefit-risk assessment remains favorable for patient to participate in this trial, even under the situation of the current COVID-19 pandemic. The operation of LPS16763 will allow enrolled AD patients the opportunity to receive a therapy which may provide benefit in improving their itch sensations, overall disease severity, and QoL.

Healthy participants will not benefit directly from participation in this study, other than the nominal reimbursements provided for completing study procedures and visits. However, the results obtained from healthy volunteers in comparison with AD patients will allow the Sponsor to better understand the epidermal defects observed in AD patients. Participating in a clinical trial like this may expose healthy subjects to a higher risk to any type of infection including COVID-19. Investigators will implement safeguards to reduce the risk for any study participant to become infected during the study.

The Sponsor also recognizes that the “COVID-19” pandemic may have an impact on the conduct of clinical trials. The Sponsor will monitor the situation closely and ensure the integrity of the trial conduct and data (see Section 8).

2.3.5 Overall benefit: risk conclusion

The potential risks identified in association with dupilumab treatment and skin biopsy collection are justified given the measures taken to minimize risk to study participants participating, the excellent safety profile and clinical experience with dupilumab and the anticipated benefits that may be afforded to participants with AD.

For healthy participants no benefit is expected, but there is also no relevant risk identified for those participants given investigator safeguards.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Assess change in neuronal architecture following long term treatment with dupilumab in skin biopsies from AD participants with chronic pruritus	• Change from baseline on Week 17 for intraepidermal nerve fiber density by protein gene product 9.5 (PGP9.5) antibody staining in lesional skin • Change from baseline on Week 17 for nerve fiber branching by PGP9.5 antibody staining in lesional skin
Secondary	
• Assess change in neuronal architecture following short term treatment with dupilumab and during follow-up in skin biopsies from AD participants with chronic pruritus	• Changes from baseline on Weeks 3 and 21 for intraepidermal nerve fiber density by PGP9.5 antibody staining in lesional skin • Changes from baseline on Weeks 3 and 21 for nerve fiber branching by PGP9.5 antibody staining in lesional skin
• To evaluate the efficacy of dupilumab in AD participants with chronic pruritus	• Changes from baseline over time and at Weeks 17 and 21 for the outcomes of the following assessments/questionnaires: - Peak pruritus assessed by numeric rating scale (NRS) - Eczema and severity index (EASI) - Scoring Atopic Dermatitis (SCORAD) - Patient-Reported Outcomes Measurement Information (PROMIS-itch) - Patient Oriented Eczema Measure (POEM) - Dermatology Life Quality Index (DLQI) - Atopic Dermatitis Control Tool (ADCT) - Sleep quality NRS - Skin Pain NRS - Skin Sensitivity NRS - Skin Burning NRS • Proportion of AD participants reaching pruritus NRS ≥4 point improvement from baseline at Weeks 3, 5, 9, 17, and 21
• To evaluate the safety of dupilumab in adult participants with moderate-to-severe AD	• Incidence of treatment-emergent adverse events during treatment and follow-up period
Exploratory	
• Assess change in neuromarkers following treatment with dupilumab in skin biopsies from AD participants with chronic pruritus	• Nanostring-Digital Spatial Profiling (N-DSP) for epidermal proteins and RNA changes from baseline in lesional skin on Weeks 3, 17, and 21

Objectives	Endpoints
	• Neuromarkers[a] changes from baseline on Weeks 3, 17, and 21 in lesional skin (detected by immunohistochemistry, RNA in situ hybridization and/or RT-qPCR): - NGF - NK-1R - MRGPRX1/2/4 - TRPV1/A1 - SEMA3A - integrin alpha 6 - periostin - ANO1 - NTRK1 - NRTN - IL-4 - IL-13 - IL-31 - Mast cells, basophils, eosinophils, keratinocytes, macrophages and lymphocytes
• Compare the neuronal architecture and neuromarkers in skin biopsies of AD lesions and normal healthy skin	• Neuronal architecture in lesional skin biopsies from AD patients and skin biopsies from healthy controls at baseline • Neuromarkers in lesional skin biopsies from AD patients and skin biopsies from healthy controls at baseline
• Compare the neuronal architecture and neuromarkers in skin biopsies of lesional skin from AD patients with biopsies from non-lesional skin	• Neuronal architecture in lesional and non-lesional skin biopsies from AD patients at baseline • Neuromarkers in lesional and non-lesional skin biopsies from AD patients at baseline
• Compare the treatment related outcomes for neuronal architecture and neuropmarkers with outcomes of clinical assessments of AD (clinician- and patient-reported outcomes)	• Neuronal architecture, Nanostring derived parameters and neuromarkers changes from baseline and clinical assessments changes from baseline

a For gene IDs refering to neuromarkers see Section 8.3.3

3.1 APPROPRIATENESS OF MEASUREMENTS

The clinical outcome assessments to be applied in this study are a panel of valid, robust, and frequently used questionnaires and PROs scales. The appropriateness of these variables has been demonstrated in many clinical studies with dupilumab.

Skin biopsy collection and processing via RNAlater and formalin fixation/paraffin embedding are standard and frequently used practices. Neuromarkers will be assessed through a battery of standard molecular biology methods including immunohistochemistry (IHC), RNA in situ hybridization (ISH) and reverse transcription-quantitative polymerase chain reaction (RT-qPCR), the appropriateness of these measurements have been described extensively. Nanostring-DSP is a new technology that allows for multiplex digital spatial molecular profiling of proteins and/or RNA in tissue or blood samples which allows for high resolution, tissue-specific understanding of the way in which inflammatory cells and signaling pathways are altered with dupilumab treatment (8).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, interventional, single-arm, non-controlled, multi-center exploratory study to evaluate the effect of dupilumab on neuronal architecture and neuronal markers in skin biopsies of lesional and non-lesional skin and compare these results with PROs and clinical assessments in approximately 34 participants with moderate-to-severe AD. Collection of skin biopsies of lesional skin at baseline and post-lesional skin at the end of treatment (EoT) (Week 17) is mandatory for all AD participants. If possible, a post-lesional skin biopsy at Week 3 and Week 21 will be collected.

Skin biopsies taken from healthy skin from healthy donors will serve as a control.

The maximum study duration for AD participants will be up to 25 weeks. The study will comprise of:

- Screening Period (Day -28 to -1): Patients will be evaluated according to inclusion and exclusion criteria. At Baseline Visit (Day 1), patients who remain eligible will be enrolled
- Treatment Period (Day 1 to Week 17): Treatment with Q2W dupilumab.
- Follow-up Period (Week 17 to Week 21): Safety follow-up period to collect data for safety and efficacy after the participant has completed the treatment period.

Atopic Dermatitis participants will be called by the Investigator around 8 weeks after the EoS Visit to assess if safety related issues have occurred during this period.

Healthy participants will undergo a Screening Period of 21 days and a 7 days Observational Period following collection of the skin biopsy.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The most suitable population to investigate effects of dupilumab on itch and related neuronal changes and neuromarkers are patients with moderate-to-severe AD. This is also the population for which dupilumab has been granted a marketing authorization based on positive results on itch reduction from several Phase 2 and 3 studies.

The majority of the clinical assessments (questionnaires, PROs, NRS etc) have been successfully applied in other clinical studies, while most of the planned methods and tests to evaluate effects on neuronal architecture and most of the neuromarkers have not been investigated in a clinical setting with dupilumab. It is thus not known which endpoints will change under treatment with dupilumab, as well the magnitude of an effect. Differences in the epidermal micro- and neuroanatomy between healthy and AD skin has been described recently. For example, in severely lesioned skin areas from AD patients nerve fibers reaching the upper region of the thickened epidermis were scarcely found (9). Accordingly, selection of healthy participants to serve as a control for non-lesional skin is considered justified. With respect to the study endpoints and because of the unknown outcome of dupilumab treatment on selected endpoints, the nature of the study is exploratory only. No sample size calculation will be applied nor is it planned to run confirmatory statistics for the aforementioned endpoints.

Because dupilumab is approved for the treatment of AD participants in the countries or participating investigational sites, the inclusion of a placebo group is not considered ethical. In addition, the effect on laboratory markers, if detectable, is thought to be unbiased, thus not requiring a control group.

The treatment duration of 16 weeks has been chosen based on clinical results showing evidence of itch reduction within this period of time in studies with dupilumab.

4.2.1 Participant input into design

Not applicable.

4.3 JUSTIFICATION FOR DOSE

The dose selected in this study is the dose approved for the treatment of moderate-to-severe AD patients ≥18 years of age for dupixent in the US and EU.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including end of study (EoS) visit as shown in the schedule of activity (SoA) (Section 1.3 and Section 1.4).

The end of the study is defined as the date of the last visit of the last participant in the study shown in the SoA (Section 1.3 and Section 1.4) for the last participant in the trial globally.

5 STUDY POPULATION

A total of 34 AD participants with moderate-to-severe AD and up to 10 healthy participants are to be enrolled in this study. Drop-outs will not be replaced.

Inclusion of healthy participants should be matched for age, gender, race, and anatomical site of skin biopsy. Accordingly, inclusion of healthy participants will start after enrolment of AD participants has been completed. The algorithm for matched healthy participants inclusion will be provided in a separate document.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply.

5.1.1 Atopic dermatitis patients

Age

I 01. Male or female of ≥18 years of age inclusive, at the time of signing the informed consent form (ICF).

Type of participant and disease characteristics

I 02. Diagnosed with moderate-to-severe chronic AD for at least 1 year before screening.

I 03. Eligible to be treated with dupilumab according to product monograph.

I 04. Pruritus lasting 6 or more weeks before baseline (Day 1).

I 05. Eczema Area and Severity Index (EASI) score ≥12 at baseline.

I 06. Pruritus numerical rating scale (NRS) ≥4 at baseline.

I 07. Investigator global assessment (IGA) score of ≥3 at screening (on the 0 to 4 scale) at baseline.

I 08. Atopic dermatitis active lesions on the upper limbs or lower limbs suitable for a skin biopsy without oozing, bleeding, or infection on upper limbs or trunk.

I 09. Patients with acute AD lesions as determined by Investigator’s judgment.

I 10. Participants able to accept skin biopsy procedure.

I 11. Participants willing to refrain from applying any emollients or topical medications on the target assessment areas (including lesional and non-lesional) throughout the study unless necessary to treat intolerable symptoms.

I 12. Participants willing and able to comply with all site visit and study-related procedures.

I 13. Participants able to understand and complete all patient related outcome assessments and questionnaires.

Concomitant medication

I 14. Stable treatment with non-prohibited medication (Section 6.5.2) or therapy during the study.

Informed consent

I 15. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.1.2 Healthy participants

I 01. Male or female of ≥18 years of age inclusive, at the time of signing the ICF.

I 02. Certified as generally healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination). Well-controlled underlying medical conditions are allowed as long as they do not interfere with assessments or objectives of this study (eg, neurological diseases, neuropathy, skin diseases, chronic pruritus, etc).

I 03. Participants able to accept skin biopsy procedure.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

5.2.1 Atopic dermatitis patients

Medical conditions

E 01. Previous treatment with dupilumab stopped within 6 months of baseline due to inadequate response to dupilumab.

E 02. Skin conditions other than AD that can confound assessments in the opinion of the investigator (ie, skin atrophy, severe photo damage).

E 03. Regular use (>2 visits per week) of a tanning booth/parlor within 4 weeks of the Screening Visit.

E 04. 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 participants with short life expectancy, participants with uncontrolled diabetes (hemoglobin A1c ≥9%), participants with cardiovascular conditions (eg, Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, participants on dialysis, nephropathy), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, psychiatric, or lymphatic diseases.

E 05. Patients with active tuberculosis (TB) or non-TB mycobacterial infection, or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the participant 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 will be performed on a country by country basis, according to local guidelines if required by regulatory authorities or ethics boards.

E 06. Diagnosed with, suspected of, or at high risk of endoparasitic infection, and/or use of antiparasitic drug within 2 weeks before the Screening Visit (Visit 1) or during the Screening Period.

E 07. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before the Screening Visit (Visit 1) or during the Screening Period.

E 08. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the Investigator.

E 09. Active malignancy or history of malignancy within 5 years before the Baseline Visit, except completely treated in situ carcinoma of the cervix and completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

E 10. Ocular disorder that in the opinion of the Investigator could adversely affect the individual's risk for study participation. Examples include, but are not limited to, individuals with a history of active cases of herpes keratitis, Sjogren's syndrome, keratoconjunctivitis sicca or dry eye syndrome that require daily use of supplemental lubrication or individuals with ocular conditions that require the use of ocular corticosteroids or cyclosporine.

E 11. History of systemic hypersensitivity or anaphylaxis to dupilumab or any other biologic therapy, including any excipient.

E 12. Known or suspected alcohol and/or drug abuse.

E 13. Participant with any other medical or psychological condition including relevant laboratory or electrocardiogram abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant 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 participants excluded under this criterion will be noted in study documents (chart notes, electronic case report form [eCRF], etc).

Sex

E 14. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

E 15. Women of childbearing potential (see Section 10.4.1) unwilling to use adequate birth control.

Adequate birth control is defined as agreement to consistently practice an highly effective and accepted method of contraception throughout the duration of the study and for 12 weeks after last dose of study drug (see Section 10.4.2).

Prior/concomitant medication or therapy

E 16. Intake of any prohibited prior or concomitant medication as specified in Section 6.5.2.

E 17. Planned or anticipated use of any prohibited medications and procedures during screening and study treatment period.

Diagnostic assessments

E 18. Participants with any of the following result at the Screening Visit (Visit 1):

- Positive (or indeterminate) hepatitis B surface antigen (HBsAg) or,
- Positive total hepatitis B core antibody (HBcAb) confirmed by positive hepatitis B virus (HBV) DNA or,
- Positive hepatitis C virus antibody (HCVAb) confirmed by positive hepatitis C virus (HCV) RNA.
- Positive human immunodeficiency virus (HIV) 1/2 serology or history of HIV infection or at the Screening Visit (Visit 1).

Other exclusions

E 19. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 20. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 21. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-Good Clinical Practice [GCP] Ordinance E6).

E 22. Any specific situation during study implementation/course that may rise ethics considerations.

E 23. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 24. Participants suffering from an ailment that makes taking repeat biopsies difficult (blood dyscrasias, anticoagulative use, allergy to local anesthetics etc) or if participant has tattoos at locations of biopsy.

5.2.2 Healthy participants

E 01. Regular use (>2 visits per week) of a tanning booth/ parlor within 4 weeks of the Screening Visit.

E 02. Treatment with the following concomitant medications and procedures is prohibited within 4 weeks before the Screening Visit or 5 half-lives (whichever is longer) until EoS Visit:

- Topical medication.
- Analgesics.
- Immunomodulators.
- Antidepressants.
- Anti-anxiety drugs.

E 03. Any Type 2 immune disorders (including, but not limited to atopic dermatitis or asthma), uncontrolled Type 2 diabetes mellitus, Type 1 diabetes mellitus, neuropathy or any other neurological disease.

E 04. Any concomitant illness(es) or conditions that, in the Investigator's judgment, would adversely affect the subject's participation in the study or potentially affect any skin biopsy related read out.

E 05. Positive test for immunoglobulin E (IgE) antibodies.

E 06. Known or suspected alcohol and/or drug abuse.

5.3 LIFESTYLE CONSIDERATIONS

- Non-prohibited concomitant medication or therapy should be kept stable during the study; any changes of concomitant medication should be recorded in the eCRF.
- Participants should not apply any emollients on or within 5 cm of the predefined skin assessment areas during the entire study period.

5.3.1 Meals and dietary restrictions

- Participants with a known food allergy should not consume any foods from an outside home provider on the day of the dupilumab injection.
- Alcohol is prohibited for at least 16 hours before each visit and each clinical assessment (if done at home).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are subsequently found to be not eligible to enroll in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious AE (SAE).

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Rescreening may be allowed once during the open screening period and upon the Investigator's decision (for certain circumstances, eg, participants cannot start the study due to private reasons). All screening procedures will have to be repeated and a different patient identification number will be assigned. There is no requirement for a waiting period between the screen failure date and the rescreening date. Participants who are rescreened must sign a new consent form and all Visit 1 procedures must be repeated.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Study participants will be assigned to study intervention as described below:

- Up to 34 patients with moderate-to-severe AD will receive dupilumab.
  - Dose regimen: Participants will receive a SC loading dose of dupilumab 600 mg on Day 1, followed by Q2W SC dosing of dupilumab 300 mg (2 mL of a 150 mg/mL solution) from Week 3 to Week 15.

One kit number list is generated centrally by Sanofi and IMP is packaged in accordance with this list.

Study intervention will be dispensed at the study visits summarized in SoA (see Section 1.3). Returned study intervention should not be re-dispensed to the participants.

Table 2 - Overview of study interventions administered

ARM name	Dupilumab
Intervention name	Dupilumab 300 mg
Type	Biological
Dose formulation	A 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in 2 mL
Unit dose strength(s)	300 mg
Dosage level(s)	300 mg every 14 ±2 days after an initial loading dose of 600 mg
Route of administration	Subcutaneous[a]
Use	Experimental
IMP	IMP
Packaging and labeling	Each dose of dupilumab will be supplied as 1 glass prefilled syringe packed in a patient kit box. Both glass prefilled syringe and the box will be labeled as required per country requirement.
Storage	2°C to 8°C
Current/Former name(s) or alias(es)	Dupixent

a Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site is not injected twice during consecutive administrations. Injection in the upper arms can only be done by the study site staff and/or by a trained person or health care professional but not the participant themselves. Site of injection should be locally distant from the site of skin biopsies.

Investigational medicinal product

The IMP will be administered every 14 ±2 days (Q2W) during the 16-week treatment period (with the last IMP administration at Week 15).

For the doses that are not scheduled to be given at the study site, administration of IMP at participant's home is allowed after appropriate training of the participant (or parent/legally authorized representative/caregiver). At Visit 2, the Investigator or delegate will prepare and inject the first dose of IMP in front of the participant (or parent/legally authorized participant representative/caregiver). The participant (or parent/legally authorized representative/caregiver) will prepare and inject the second dose of IMP at Visit 3 under the supervision of the Investigator or delegate. The training must be documented in the participant's study file.

In case of emergency (eg, natural disaster, pandemic, etc) different methods of IMP injection training (eg, training remotely with instructions provided by phone, etc) can be performed (and will be documented in the participant's study file). If the participant (or parent/legally authorized representative/caregiver) is unable or unwilling to prepare and inject IMP, injections can be performed at the study site by way of unscheduled visits; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP at participant's home.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits in case of emergency (eg, natural disaster, pandemic, etc), IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

When the participant has a study visit, the IMP will be administered following clinical procedures and blood collection. Participants should be monitored for at least 30 minutes. The monitoring period may be extended as per country-specific or local site-specific requirements.

Participant/parent/legally authorized representative/caregiver should be trained by the site staff to recognize potential signs and symptoms of hypersensitivity reaction in order to self monitor/monitor at home following injection. In case of hypersensitivity symptoms, the participant should contact their healthcare provider or emergency services.

Subcutaneous injection sites should be alternated among the 4 quadrants of the abdomen (avoiding navel and waist areas), the upper thighs or the upper arms, so that the same site is not injected between two Q2W injections. Injections in the upper arms could be done only by a trained person (parent/legally authorized representative/caregiver trained by Investigator or Delegate) or health care professional but not the participants themselves. Site of injection should be locally distant from the site of skin biopsies.

For doses not given at the study site, eDiary will be provided to record information related to the injections. The eDiary will be kept as source data in the participant's study file.

6.1.1 Devices

No devices for administration of study drug will be used in this study.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Storage and handling

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. At site, all study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. During transportation from the study site to the participant's home and at the participant's home, study intervention must be handled/stored as per instructions of the Study Drug Transportation Guidelines and the Patient User Instruction Manual. Participant/parent/legally authorized representative/caregiver should be trained by the site staff to ensure that IMP is handled and stored properly at participant's home.
4. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.2.2 Responsibilities

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.5.9).

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 the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for Direct-to-Patient (DTP) shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The study is open-label study without a treatment control or placebo group in patients. To control bias, the following measures are taken:

- Healthy participants will serve as a reference comparator group for interpreting study results.
- PROs will be collected by electronic data capture.
- Efficacy data will be measured by the same device model.
- Biomarker data will be measured by an experienced laboratory.
- Study is limited to 2 to 4 very experienced study centers.
- Standardized study assessment procedures.
- Standardized photography for targeted lesional areas, and clinical disease severity and PRO evaluations.
- Reason for screen failures (if any) will be documented.

6.4 STUDY INTERVENTION COMPLIANCE

Investigator or his/her delegate must ensure that IMP will be administered to each participant according to the labeling instructions.

IMP accountability:

- Intervention units are returned by the participant at the next study visit. In case of DTP emergency process, the intervention units can be returned by the carrier (if defined in the contract).
- The Investigator counts the number of remaining unused kits/pre-filled syringes, and fills in the IMP accountability and inventory forms.
- The Investigator or his/her delegate records the dosing information on the appropriate page(s) of the eCRF.
- The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and source documents.

When participants are dosed at the site (see Section 1.3), they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home (see Section 1.3), they will document compliance on a home dosing diary. Compliance with study intervention will be assessed at each visit. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.5 CONCOMITANT THERAPY

Any allowed medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, [live vaccine is prohibited]) that the participant is receiving at the time of enrolment or receives during the study must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Any change in concomitant medication must be recorded.

Participants must abstain from taking prohibited prescription drugs within 4 weeks before the Screening Visit or 5 half-lives (whichever is longer) until the Week 21 (EoS Visit), unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Paracetamol/acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study, except for 12 hours prior to a visit or clinical assessment to prevent any bias to itch related PRO assessments. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Sponsor representative(s), if required.

6.5.1 Rescue medicine

During Treatment Period, if medically necessary (ie, to control intolerable AD symptoms on face and genital areas), rescue treatment for AD may be provided to participants at the discretion of the Investigator (ie, topical treatment with high potency topical corticosteroids [TCS]). Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety laboratory assessments) immediately before administering any rescue treatment. An unscheduled visit may be used for this, if necessary.

Investigators will be required to perform an IGA evaluation prior to starting rescue treatment and initiate rescue treatment only in patients who either have an IGA score of 4, or have intolerable AD symptoms. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF.

6.5.2 Prohibited medications and procedures

Treatment with the following concomitant medications and procedures is prohibited within 4 weeks before the Screening Visit or 5 half-lives (whichever is longer) until the Week 21 (EoS Visit):

1. Topical treatment used for the treatment of AD or for super-infection:
    - Topical calcineurin inhibitors (tacrolimus or pimecrolimus).
    - Topical phosphodiesterase inhibitors (crisaborole).
    - Topical corticosteroids.

2. Topical antibiotics.
3. Topical immunosuppressive/immunomodulating treatment.
4. Monoclonal antibodies (mAbs) within 5 half-lives or within 6 months before the Screening Visit if the half-life is unknown.
5. Antihistaminic medication, H2 receptor antagonists.
6. Systemic treatment for AD with an immunosuppressive/immunomodulating agent (including, but not limited to, systemic corticosteroids, cyclosporine A [CsA], azathioprine [AZA], methotrexate [MTX], mycophenolate mofetil [MMF], Interferon gamma [IFN-γ], or other biologics).
7. Biologic therapy/systemic immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc).
8. Treatment with immune modulating biologics including, but not limited to, the following:
   - Any cell-depleting agents (eg, rituximab).
   - Infliximab, adalimumab, golimumab, certolizumab pegol, abatacept, etanercept, or anakinra.
9. Leukotriene antagonists/modifiers within, unless patient is on a continuous treatment for at least 4 weeks before the Screening Visit.
10. Antifibrinolytic tranexamic acid or epsilon-aminocaproic acid.
11. Intravenous immunoglobulin (IVIG) therapy and/or plasmapheresis.
12. Procedures used for the treatment of AD:
    - Phototherapy (such as ultraviolet B [UVB], narrowband UVB [NBUVB], ultraviolet A1 [UVA1], or psoralen-UVA [PUVA]).
    - Bleach baths.
    - Use of a tanning booth/parlor.

For patients having participated recently in a clinical study with an investigational new drug which is not approved in the specific country concerned and for which the PK or pharmacodynamic half-life is not known, the wash out period between last intake of investigational new drug and screening visit should be ≥6 months.

In addition, participants will be asked to abstain from live (attenuated) vaccinations through Week 21. If a participant requires a vaccination prior to 12-weeks after discontinuing treatment with dupilumab, titers should be checked post-vaccination. Live (attenuated) vaccinations include but are not limited to the following:

- Bacillus Calmette-Guérin (BCG).
- Chickenpox (Varicella).
- FluMist-Influenza.

- Intranasal influenza.
- 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.

NOTE: For participants who have vaccination with live attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the EoS, or preponed to before the start of the study without compromising the health of the participant:

- Patient for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
- Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

6.5.3 Permitted medications

Other than the prohibited medications and procedures listed in Section 6.5.2, treatment with concomitant medications and procedures is permitted during the study. This includes nasal and inhaled corticosteroids. The use of these medications should be recorded.

6.6 DOSE MODIFICATION

No change in IMP dose is allowed. Patients who discontinue treatment with IMP will be excluded from further participation.

6.7 TREATMENT OF OVERDOSE

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for a reasonable period of time.
3. Document appropriately in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

6.8 INTERVENTION AFTER THE END OF THE STUDY

Any intervention after the EoS Visit will be at the discretion of Investigator or treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will be asked to remain in the study to be evaluated for clinical assessments (including PRO) and collection of a skin biopsy.

Pregnancy in a female participant will lead to definitive intervention discontinuation in all cases.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures 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.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (eg, natural disaster, pandemic, etc) (see Section 6.1). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

Temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the participant.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study. 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 reason(s) for treatment discontinuation and this should be documented in the eCRF.

The Investigators should discuss with them about the key visits to be attended. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

Drop-outs will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3 and Section 1.4). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3 and Section 1.4), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3 and Section 1.4).
- Assessments performed only at the Screening and/or Baseline Visit include medical history, medication history, serology, demographics, and diagnosis of chronic AD. Atopic dermatitis disease characteristics are assessed by clinical and PRO assessments.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 100 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In light of the public health emergency related to COVID-19 (or in case of any other public health emergency), the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, such as phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff. Implementation of such mechanisms may differ country-by-country, depending on country regulations and local business continuity plans. Additionally, no waivers to deviate from protocol enrolment criteria due to COVID-19 (or any other pandemic) will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 (or any other public health emergency) and will remain in effect only for the duration of the public health emergency.

8.1 EFFICACY ASSESSMENTS

Clinical efficacy will be assessed through patient-reported outcome (PRO) and clinician reported outcomes (ClinRO) scales in AD participants only.

The PRO questionnaires (including NRS) should be completed by the patients and before the skin biopsy collection and/or any clinical tests, and before the consultation at each visit in a quiet place. The questionnaires should be completed by the patients themselves, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives.

Patient-reported outcomes will be collected in an appropriate form, for which the respective device, diary and/or instruction is handed out to the patient at the Baseline Visit. During the Screening Visit the Investigator should inform participants about the PROs and devices used during the study and should examine whether the participant is capable to understand and fill out the PRO assessments and can follow the instructions provided. This is particularly important if, the Investigator has doubts about a participant's skills to read and understand the PROs eg, in case the participant does speak fluently the language used for the PROs.

Clinician reported outcomes will be completed by the Investigator or sub-investigator.

8.1.1 Patient-reported outcome (PRO) scales

8.1.1.1 Peak pruritus assessed by numeric rating scale (NRS)

The Peak Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period. Patients will be asked to rate their worst itch on a 0 ("No itch") to 10 ("Worst itch imaginable") NRS by answering the following question: "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?"

The peak pruritus NRS has been already validated in AD adult patients; a threshold for clinically relevant, within-person response was found to be ≥2 to 4-point change (10).

Peak pruritus NRS will be assessed daily during the first 28 days of treatment and weekly from Day 29 onwards until EoS period (see Section 1.3).

The Pruritus NRS will be provided in the study reference manual.

8.1.1.2 Patient-reported outcomes measurement information (PROMIS)-itch

The Patient-Reported Outcomes Measurement Information System ([PROMIS], www.healthmeasures.net) for the assessment of itch, was recently developed (11) and represents a novel suite of PRO measures for itch. The PROMIS-Itch includes several item domains to assess different aspects of the burden of chronic itch. The PROMIS-Itch item domains have good concurrent, convergent, and discriminant validity with itch intensity, good internal consistency, and no floor or ceiling effects among US adults with chronic itch.

For this study the following item domains or scales will be used. The short form version will be applied, if available.

- Itch-Severity

  The PROMIS item pool assesses the characteristics of itch, including intensity, frequency and time of occurrence. It is universal rather than disease-specific. It includes 8 items, each individually scored. There is currently no summary score.

- Itch-Activity and Clothing

  The PROMIS-Itch-Activity and Clothing item bank assesses Activity and Clothing related QoL impairment from itch (pruritus) in adults. It is universal rather than disease-specific. It assesses the impact of itch over the past 7 days. For this item the short version will be used.

- Itch-Mood and Sleep

  The PROMIS-Itch-Mood and Sleep item bank assesses mood and sleep related QoL impairment from itch (pruritus) in adults. It is universal rather than disease-specific. It assesses the impact of itch over the past 7 days. For this item the short version will be used.

- Itch-Interference

  The PROMIS-Itch-Interference item bank assesses general issues related to QoL impairment from itch (pruritus) in adults. It is universal rather than disease-specific. It assesses the impact of itch over the past 7 days. For this item the short version will be used.

- Itch-Scratching Behavior

  The PROMIS-Itch-Scratching Behavior scale assesses QoL impairment from scratching behavior and the physical manifestations of itch (pruritis) in adults. It is universal rather than disease-specific. It assesses the impact of itch over the past 7 days.

- Itch-Quality

  The PROMIS-Itch-Quality item pool assesses the subjective description of the sensation of itch with a 16-item checklist. Respondents can select as many as apply. There is no summary score.

- Itch-Triggers

  The PROMIS-Itch-Triggers item pool assesses the subjective description of the triggers of itch with a 13-item checklist. Respondents can select as many as apply. There is no summary score.

The PROMIS-Itch will be assessed at timepoints according to Section 1.3.

The PROMIS-Itch will be provided in the study reference manual.

8.1.1.3 Patient oriented eczema measure (POEM)

The Patient Oriented Eczema Measure (POEM) is a 7-item, PRO questionnaire used in clinical practice and clinical trials to assess frequency of disease symptoms in children and adults (28). 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 severity, with higher score indicating higher severity.

The POEM will be assessed at time points according to Section 1.3.

The POEM will be provided in the study reference manual.

8.1.1.4 Dermatology life quality index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item, PRO questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QoL (12, 13). The questionnaire has a "past week" recall period and has an overall scoring system of 0 to 30; a high score is indicative of a poor QoL. The questionnaire will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).

The DLQI will be assessed, at time points according to Section 1.3.

The DLQI is provided in the study reference manual.

8.1.1.5 Atopic dermatitis control tool (ADCT)

The Atopic Dermatitis Control Tool (ADCT) is a PRO questionnaire designed to assess patient-self-perceived control of their eczema in clinical practice and in research settings (14). It is validated in adult and adolescent patients with AD (15). The ADCT contains 6 items allowing a comprehensive coverage of the dimensions defining AD control, ie, overall severity of AD symptoms, frequency of intense episodes of itching, extent of AD related bother, impact on sleep, impact on daily activities, impact on mood or emotions. Recall period is 1 week. Each item of the ADCT is rated from 0 to 4 Likert scale and is equally weighted, thus resulting in a total score from 0 to 24; higher scores indicate lower AD control.

A threshold value equal or at least 7 on the ADCT total score has been established to define the cut off for patients with poorly controlled AD (14). A responder definition of 5 points on the ADCT total score has been defined as the meaningful within-person change threshold (15).

The ADCT will be assessed at time points according to Section 1.3.

The ADCT will be provided in the study reference manual.

8.1.1.6 Skin pain numerical rating scale

Skin pain NRS is a one-item PRO measure asking the patients to rate their skin pain using a 0 ("No pain") to 10 ("Worst pain possible") NRS. Patients will be asked the following question:

"Think about all the areas of your skin with eczema. How would you rate your skin pain at its worst in the past 24 hours?"

The skin pain NRS will be assessed at time points according to Section 1.3.

The skin pain NRS is provided in the study reference manual.

8.1.1.7 Skin sensitivity to touch numerical rating scale

Skin sensitivity to touch NRS is a 1 item PRO measure asking the patients to rate their skin sensitivity to touch using a 0 (“Normal”) to 10 (“Extremely sensitive”) NRS.

Participant will be asked the following question: "Think about all the areas of your skin with eczema. How sensitive was your skin at its worst in the past 24 hours?”

The skin sensitivity to touch NRS will be assessed at time points according to Section 1.3.

The skin sensitivity to touch NRS is provided in the study reference manual.

8.1.1.8 Skin burning numerical rating scale

Skin burning NRS is a one-item PRO measure asking patients to rate the burning sensation of their skin in the past 24 hours using a 0 (“Not at all”) to 10 (“Very much”) NRS.

Patient will be asked the following question: “Think about all the areas of your skin with eczema. How much did your skin burn at its worst in the past 24 hours?”

The skin burning NRS is provided in the study reference manual.

8.1.1.9 Sleep quality numerical rating scale

Sleep quality NRS is a one-item PRO measure asking patients to rate the quality of their sleep using a 0 (“Worst possible sleep”) to 10 (“Best possible sleep”) NRS. Patients will be asked to complete the following question upon awakening:

“Select the number that best describes the quality of your sleep last night.”

The Sleep Quality NRS will be assessed at time points according to Section 1.3.

The sleep quality NRS is provided in the study reference manual.

8.1.2 Clinician reported outcomes (ClinRO) questionnaires

8.1.2.1 Investigator global assessment (IGA)

The IGA is a ClinRO 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 Screening also and is used as one of the inclusion criteria for determining patient’s eligibility.

The IGA will be provided in the study reference manual.

8.1.2.2 Eczema and severity index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (16). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, and edema], scratching [excoriation], and lichenification) will each be assessed for severity by the Investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

The EASI assessment tool will be provided in the study reference manual.

8.1.2.3 Scoring atopic dermatitis (SCORAD)

The Scoring Atopic Dermatitis (SCORAD) is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (17). The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation).

Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5+7B/2+C.

The SCORAD will be assessed at time points according to Section 1.3.

The SCORAD assessment tool will be provided in the study reference manual.

8.2 STANDARDIZED PHOTOGRAPHS

In AD participants, a picture of high resolution will be taken of a representative area of AD involvement (the lesional area used for skin biopsy collection) on Day 1 (predose). Subsequent pictures of the same area will be taken as described in Section 1.3.

Photography will be done for healthy participants on Day 1.

8.3 EXPLORATORY ASSESSMENTS AND BIOMARKERS

Two Skin biopsies will be collected once in healthy participants and repeatedly (at least twice; baseline and Week 17) from lesional and post-lesional skin in AD participants for exploratory assessments and a broad panel of biomarkers. Further biopsies from post-lesional and non-lesional skin are optional for AD participants.

8.3.1 Skin biopsy samples

Skin biopsies of 4 mm diameter each will be collected from healthy participants and AD participants at time points according to the SoA (Section 1.3). Study staff will provide instructions regarding suture removal, if sutures are used for closure.

Gelfoam®, a hemostatic, can be applied for biopsy closure. Study staff will notify the patient this will dissolve and provide instructions regarding wound dressing and care.

The skin biopsy samples will serve to study the neuronal architecture (neuroanatomy) and neuromarkers in the epidermis of pruritic lesional skin before start of treatment with dupilumab and localisation matched post-lesional healing skin areas after EoT with dupilumab in AD participants. Accordingly, the collection of 4 biopsies in total is mandatory for AD participants at the following timepoints:

- Baseline: 2 biopsies of 4 mm diameter each at baseline before start of treatment from pruritic lesional skin.
- Week 17: 2 biopsies of 4 mm diameter each from non-pruritic, post-lesional healed or healing skin, with localisation matched to the baseline pruritic lesional biopsy.
  - if post-lesional healed skin that is completely non-pruritic non-lesional is not available at later visits, one of the following biopsies should be collected (in the order of relevance): 1. lesional non-pruritic skin, 2. Post-lesional pruritic skin or 3. lesional pruritic skin.

Participants who refrain from providing these biopsies at baseline and Week 17 are not eligible for this study.

Collection of the following additional biopsies is optional for AD patients, including

- 2 biopsies of 4 mm diameter each from non-pruritic, post-lesional healed or healing skin, localisation matched to the baseline pruritic lesional biopsy, at week 3 and at the end of the observation period at Week 21.
  - if post-lesional healed skin that is completely non-pruritic non-lesional is not available at later visits, one of the following biopsies should be collected (in the order of relevance): 1. lesional non-pruritic skin, 2. Post-lesional pruritic skin or 3. lesional pruritic skin.
- 2 biopsies of 4 mm diameter each from *non-lesional skin* at baseline.

Healthy participants will provide 2 biopsies of 4 mm diameter each only. These biopsies serve as a control and will allow to investigate differences in neuroanatomy and neuromarkers between lesional skin from AD participants and normal skin. Skin biopsies must be taken from non-lesional healthy skin. Taking biopsies from an area adjacent to any skin lesion (inflamed skin, sun burn, acne, etc) must be avoided.

Each skin biopsy will be cut and divided in 2 slices of approximately equal size.

If 2 biopsies were taken at the same time (which is mandatory for healthy participants and AD participants at baseline and Week 17), the corresponding 4 slices (#A, B, C and D) will be processed as follows immediately after collection:

A) Fixation with paraformaldehyde (PFA) and freeze at -70°C

B) Transfer into RNAlater solution and store at -70°C

C) Fixation with 10% neutral buffered formalin (NBF), embed into paraffin, and store at 4°C

D) Fixation with 10% NBF, embed into paraffin, and store at 4°C

The samples will be processed for RNA-ISH, RT-qPCR, neuroanatomy, IHC, and Nanostring-Digital Spatial Profiling (N-DSP).

Detailed instructions for sample collection and handling are provided in the study reference manual.

Unused skin material will be returned from laboratories assigned for the different methods to a facility selected by the sponsor and stored under appropriate conditions for future use (Section 8.8)

8.3.2 Neuroanatomy/Neuronal architecture

#A skin biopsy samples will be investigated for epidermal neuroanatomy/neuronal architecture. Briefly, the PFA-fixed part of the biopsies will be used to analyze the epidermal nerve fiber density and anatomy. Nerve fibers will be visualized by staining consecutive sections for the pan-axonal marker protein gene product 9.5 (PGP9.5); the basement membrane will be visualized by staining for collagen type 4 in order to determine exactly the point of invasion of nerve fibers into the epidermis.

Quantification of intraepidermal nerve fiber density will be calculated by assessing nerve fibers crossing the basement membrane per square millimetre (F/mm^2).

Branching of epidermal nerve fibers will be assessed semi-quantitatively by classifying patients into 4 groups comprised of only linear, mainly linear, mainly branched or only branched fibers.

8.3.3 Reverse transcription quantitative PCR (qRT-PCR)

#B skin biopsy samples will be investigated by qRT-PCR for a panel of epidermal neuro- and inflammatory markers including (corresponding gene IDs provided in brackets):

- NK-1R (*TACR1*)
- MRGPRX1 (*MRGPRX1*)
- MRGPRX2 (*MRGPRX2*)
- MRGPRX4 (*MRGPRX4*)
- TRPV1 (*TRPV1*)

- TRPA1 (*TRPA1*)
- Periostin (*POSTN*)
- Integrin alpha 6 (*ITGA6*)
- Anoctamin -1 (*ANO1*)
- TRKA (*NTRK1*)
- Neurturin (*NRTN*)
- IL-4 (*IL4*)
- IL-13 (*IL13*)
- IL-31 (*IL31*)

8.3.4 RNA in situ hybridization (ISH)

#C skin biopsy samples will be investigated by ISH for a panel of epidermal neuro- and inflammatory markers including (corresponding gene IDs provided in brackets):

- MRGPRX1 (*MRGPRX1*)
- MRGPRX2 (*MRGPRX2*)
- MRGPRX4 (*MRGPRX4*)
- TRPV1 (*TRPV1*)
- TRPA1 (*TRPA1*)
- NK-1R (*TACR1*)

8.3.5 Immunohistochemistry (IHC)

#C skin biopsy samples will be investigated by IHC for a panel of epidermal neuro- and inflammatory markers including

- NGF
- NK-1R
- TRPV1
- TRPA1
- SEMA3A
- Integrin alpha 6
- Periostin

These markers will be co-localized with cell type markers for mastocytes, basophils, eosinophils, macrophages, lymphocytes, and keratinocytes.

8.3.6 Nanostring-digital spatial profiling (N-DSP)

#D skin biopsy samples will be investigated by N-DSP for a broad panel of RNA and protein targets.

The purpose of this study is to characterize the neuroinflammatory response to dupilumab treatment in participants with AD. The GeoMx™ digital spatial profiling is a commercial technology that allows for the analysis in situ of up to 1,833 immune genes and 92 immune protein targets simultaneously in their tissue-based morphological context from formalin fixed paraffin embedded or fresh frozen samples (18, 19). This technology will allow us to study the spatial association of nerves and immune cells in the skin and deeply profile their phenotypes and signalling pathways throughout the course of treatment. Specific RNA and protein expression targets will be selected to identify key inflammatory cells implicated in AD pathogenesis, such as lymphocytes, eosinophils, mast cells, and macrophages; inflammatory cytokines such as IL-4, IL-5, IL-9, IL-13; signalling pathways such as NK-κB and JAK-STAT; and neuromediators and their receptors, such as histamine, proteases, opioid receptors, neurotrophins, and sodium channels. The target gene and protein list will provide a comprehensive assessment with unprecedented resolution of the effect of dupilumab on inflammatory processes in lesional tissue.

8.4 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3 and Section 1.4).

8.4.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, and neurological systems. Height and weight will also be measured and recorded.
- Signs and symptoms of hypersensitivity reaction (if any) will be documented.
- A skin focused physical examination will be performed prior to each skin biopsy assessments at time points according to SoA (Section 1.3 and Section 1.4).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.4.2 Vital signs

Vital signs will be measured for AD participants in a semi-supine position after 5 minutes rest and will include heart rate, body temperature (°C), systolic and diastolic blood pressure (mmHg).

8.4.3 Pregnancy testing/Postmenopausal females

Pregnancy testing will be performed for all female AD participants of childbearing potential. Urine pregnancy (β-HCG) testing will be performed at time points according to SoA (Section 1.3). In case of positive urine test the study treatment will be withheld and a serum pregnancy test should be performed as soon as possible, to confirm the pregnancy.

Women will be tested for their FSH concentration in blood in case their postmenopausal status is not confirmed otherwise.

8.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.5.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3 and Section 1.4).

All AEs will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3 and Section 1.4).

All SAEs and adverse event of special interest (AESI) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.5.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and AEs of special interest (as defined in Section 8.5.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.5.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.5.5 Pregnancy

- Details of all pregnancies in female AD participants will be collected after the start of study intervention and until 12 weeks after EoS Visit.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.5.6 Cardiovascular and death events

Not applicable.

8.5.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.5.8 Adverse event of special interest (AD participants only)

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, modified or removed during a study by protocol amendment.

The following events are AESIs and require reporting to the Sponsor within 24 hours of learning of the event:

- Anaphylactic reactions.
- Systemic hypersensitivity reactions.
- Helminthic infections.
- Any severe type of conjunctivitis or blepharitis.
- Keratitis.
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).

The following events also require reporting to the Sponsor within 24 hours of learning of the event:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;
  - It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - 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 (See Appendix 4 [Section 10.4]).
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Symptomatic overdose (serious or nonserious) with IMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic IMP accountability checks) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.

8.5.9 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 BLOOD SAMPLE FOR EXPLORATORY RESEARCH

Venous blood samples will be collected to obtain whole blood, serum and plasma to be stored for possible future exploratory research (see Section 8.8), including genetic research.

A total of approximately 12 to15 mL venous blood will be collected per each timepoint specified in the SoA (Section 1.3 and Section 1.4) and split as follows

- 3 mL whole blood sample for DNA (K2 EDTA tube, collected at baseline only)
- 2.5 mL whole blood for RNA (Paxgene RNA collection tube)
- 4 mL whole blood for plasma
- 5 mL whole blood for serum

Storage tubes will be labelled and stored under appropriate conditions.

Blood samples for exploratory research will be collected from participants who have consented to participate in the exploratory analysis component of the study. Participation is optional. Participants who do not wish to participate in the exploratory research may still participate in the study.

Details on collection, storage and shipment of these samples will be provided in the study reference manual.

Blood samples will be collected as specified in the SoA (Section 1.3 and Section 1.4).

See Appendix 5 (Section 10.5) for information regarding genetic research.

8.8 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored

and used for future research ("research substudy") when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

Blood samples (see Section 8.7) are explicitly collected for the purpose of future research. In addition, while skin biopsies will be collected and processed for the intended use described in Section 8.3.1 these studies may not require the entirety of the tissue or processed material. With the participants separate consent, blood samples and any residual skin material remaining from planned laboratory work will be used for additional exploratory research ("research substudy") related to atopic dermatitis and related inflammatory diseases such as asthma and hidradenitis suppurativa, atopic disease processes, interleukin pathway biology, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol.

Analyses of blood and skin samples may include isolating DNA, RNA, proteins or metabolites for pharmacogenetic/genomic analysis, RNA transcriptomics (including whole transcriptome RNA sequencing), proteomics, metabolomics or lipidomics. DNA/RNA isolated from these samples will be used only to determine a possible relationship between genes and response to treatment with dupilumab, possible side effects to dupilumab and/or to study genes that may potentially be involved in atopic dermatitis and related inflammatory pathways.

Exploratory analyses may include isolation and analysis of DNA and RNA using whole genome, exome, transcriptome or targeted sequencing, or related technologies. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions. Additional proteomic analysis will utilize techniques such as enzyme-linked immunosorbent assay, Olink, mass spectrometry or related protein quantification technologies, to characterize the protein changes associated with dupilumab treatment, with AD disease conditions, or to understand related inflammatory pathways. Finally, metabolites such as lipids and other small molecules may be characterized using mass spectrometry or nuclear magnetic resonance spectroscopy.

The handling of genetic data is described in Appendix 5 (Section 10.5).

Each study participant will be informed by the Investigator about the purpose and objectives of the research substudy including future use sample storage, research analyses, and the use of coded data. In addition, each participant has to sign a separate informed consent form for the research substudy-related to future use of samples and research, and will also receive a written subject information explaining the matter.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Participants will be told that participation in this research substudy (use of samples for additional, exploratory research) and the use of their coded data for this purpose is optional and that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. In that case, biological samples will be destroyed and coded data already available will be anonymized unless otherwise required by applicable laws. Data and samples will

be used in compliance with the information provided to participants in the ICF dedicated to future research and the research substudy.

Participants who decline to participate in this optional research substudy will not provide this separate signature but are still allowed to participate in the main part of the study.

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. If required by local regularities, all participant's data and samples required for DNA or RNA transcriptome analysis will be double coded following collection of samples. Coded data and samples for additional exploratory research will be transferred to and stored by an US based central laboratory vendor chosen and contracted by the Sponsor. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal hypothesis testing is predefined in this exploratory study.

9.2 SAMPLE SIZE DETERMINATION

Sample size for this exploratory study was determined based on medical experts' input/clinical judgement. No formal sample size estimation was conducted. Approximately 10 to 12 evaluable AD participants per site might be enough to provide interpretable data and meet study primary objective.

Neuronal architecture and neuromarkers data collected from skin biopsy in similar settings as planned for this study were not available: ie, expected changes from baselines in neuronal architecture and neuromarkers after 16-week treatment with dupilumab in AD participants with chronic pruritus are unknown.

Allowing for a drop-out rate of 20%, a total of approximately 34 AD participants with chronic pruritus will be enrolled to achieve a minimum of 12 evaluable AD participants per country, ie, participants with no major or critical deviations related to IMP and/or biomarker measurements, for whom the biomarker data for primary analysis, ie, neuronal architecture and neuromarkers data from skin biopsy at baseline and Week 17, are considered sufficient and interpretable.

Up to 10 healthy participants (with a minimum of 3 per country) serving as a reference comparator group will be enrolled. Healthy participants will be matched with AD participants, as far as possible, according to site, age, gender, race, location of targeted lesional and non-lesional skin area.

Drop-out rate in healthy participants is expected to be minimal.

Any drop-out participant will not be replaced.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 3):

Table 3 - Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF
Intent-to-treat (ITT)	All enrolled patients, who received at least 1 dose of IMP and all enrolled healthy participants who have at least 1 skin biopsy performed, irrespective of compliance with the study protocol and procedures.

Population	Description
Modified ITT (mITT)	All ITT participants. If prohibited therapies for AD (see Section 6.5.3) are used and assessed by the study team as having a significant impact on skin biposy assessment, only visits prior to rescue treatment use are considered.
Safety	The safety population includes all patients, who actually received at least 1 dose of IMP or had at least 1 skin biopsy and all healthy participants who had a skin biopsy or another safety assessment performed

Abbreviations: AD: atopic dermatitis, ICF: informed consent form; IMP: investigational medicinal product; ITT=intent-to-treat, mITT: modified ITT.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be finalized prior to database lock or any interim analysis and it will include a more technical and detailed description of the statistical analyses described in this section. A specific dedicated SAP might be produced in addition to the main SAP, eg, for some or all biomarker analyses. This section is an overview of the planned exploratory statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 Participant description

9.4.1.1 Disposition of participants

A detailed description of participant accountability including count of participants by analysis populations (Table 3), screen failure participants with reasons for screen failure, participants who did not complete the study observation period along with the main reason for permanent treatment discontinuation, and participants who requested permanent treatment discontinuation, will be generated by study groups.

All withdrawals from the study, taking place on or after study intervention intake, will be fully documented in the body of the clinical study report (CSR).

A listing of subjects with treatment discontinuation will be provided.

9.4.2 Protocol deviations

During the review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, treatment compliance, prohibited therapies, and timing and availability of planned assessments. A pre-defined list of potential protocol deviations will be identified by the study team prior to the study start. The protocol deviations will then be reviewed by the study team before database lock, including missing data and study drug discontinuations, and classified as critical, major, or minor deviations.

Individual deviations to inclusion and exclusion criteria as reported by the Investigator will be listed.

If any major and critical deviations other than those involving inclusion/exclusion will be listed by participant and/or described in the body of the CSR.

9.4.3 Demographic and baseline characteristics

9.4.3.1 Participant demographic characteristics, medical history, and diagnoses

Continuous variables (age, weight) and qualitative variables (gender, race, and body mass index [BMI]) will be summarized by study groups, by descriptive statistics (summary tables) for the modified intent-to-treat (mITT) population and for additional population if relevant (eg, if many participants from the mITT population are not part of the safety population).

Specific medical/surgical history will be listed. Other baseline characteristics will be listed.

Disease characteristics at baseline: eg, ClinRO and PROs will be presented along with the on-treatment summary statistics in the Section 9.4.6.

9.4.3.2 Baseline efficacy parameters

Baseline is defined as the last available and evaluable value before and closest to the first dose of the IMP ie, at Day 1 (Visit 2, Week 1), for AD participants and as the last available and evaluable value at Screening or Day 1 (Visit 2) for healthy participants.

9.4.3.3 Baseline safety parameters

Baseline for safety parameters will be defined as the last available and evaluable value before and closest to the first dose of IMP for patients and as the last available and evaluable value at screening for healthy participants.

Baseline safety values will be presented along with subsequent safety values assessed during the study.

9.4.4 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized for patient group within the safety population.

The following listings will be provided:

- Patients receiving IMP from specified batch; (patient, IMP, and IMP batch number) will be sorted by patient.

9.4.4.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations.

If the patient's date of last dose is unknown, his/her last IMP dispensing date will be used in its place.

Duration of exposure will be summarized in patients' group using descriptive statistics such as mean, standard deviation (SD), median, minimum and maximum.

9.4.4.2 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.

Percentage of compliance for a patient will be defined as the number of administrations the patient was compliant divided by the total number of administrations the patient was planned to take (the number of doses missed due to interruptions at Investigator's judgment will not be subtracted) on or before the last IMP administration date.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, mean, SD, median, minimum, and maximum). The percentage of patients with compliance <80% will be summarized. In addition, number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%), and >20% under-planned dosing administrations.

9.4.5 Prior/Concomitant medication/therapy

Medications will be coded according to the World Health Organization Drug Dictionary (WHO Drug Dictionary, last available version before database lock). Concomitant medications with the IMP will be listed separately by participants.

9.4.6 Efficacy analyses

The efficacy evaluation will be based upon the review of the individual values (graphics), descriptive statistics (summary tables, graphics) and, where applicable, exploratory statistical analysis.

Due to the small sample size and the exploratory nature of the study, missing, or incomplete data of efficacy marker will not be imputed. In case a significant number of patients (eg, more than 20%) using rescue therapy are observed during the study Treatment Period, visit values removed due to use of rescue therapy will be imputed. The imputation methods applied will be described in the SAP.

9.4.7 Description of efficacy variables

Efficacy parameters are described in Section 8.1. The derivation of baseline results is described in Section 9.4.3.2.

The analysis of the efficacy markers will be based on the mITT population. As a sensitivity analysis, the primary endpoint will also be analyzed based on the intent-to-treat (ITT) population. Secondary endpoints analysis might be run on the ITT population as sensitivity analysis in case an important number of patients using rescue therapy is observed.

Sub-group analyses might be done, if deemed appropriate.

If relevant, based on results obtained on planned analyses (eg, if any trend or signal is observed), further exploratory analyses could be conducted, using statistical models for instance.

Analysis

Table 4 - Efficacy analyses

Endpoint	Statistical analysis methods
Primary	
• Change from baseline on Week 17 for intraepidermal nerve fiber density by PGP9.5 antibody staining in lesional skin • Change from baseline on Week 17 for intraepidermal nerve fiber branching by PGP9.5 antibody staining in lesional skin	• Raw data and change from baseline to Week 17; ie, absolute and percent changes, will be summarized with descriptive statistics (such as mean, median, SD, minimum, maximum, and 90% confidence interval) and plots for AD participants based on the mITT population
Secondary	
• Changes from baseline on Weeks 3 and 21 for intraepidermal nerve fiber density by PGP9.5 antibody staining in lesional skin • Changes from baseline on Weeks 3 and 21 for intraepidermal nerve fiber branching by PGP9.5 antibody staining in lesional skin	• Raw data and changes from baseline to Week 3 and Week 21; ie, absolute and percent changes, will be summarized with descriptive statistics (such as mean, median, SD, minimum, maximum, and 90% confidence interval) and plots for AD participants based on the mITT population • Profiles for baseline to Week 21 time points will be generated for individual values: eg, spaghetti plot and boxplot, and patients' group means
• Changes from baseline over time and at weeks 17 and 21 for the outcomes of the following assessments/questionnaires - Peak pruritus assessed by numeric rating scale (NRS) - Eczema and severity index (EASI) - Scoring Atopic Dermatitis (SCORAD) - Patient-Reported Outcomes Measurement Information (PROMIS-itch) - Patient Oriented Eczema Measure (POEM) - Dermatology Life Quality Index (DLQI) - Atopic Dermatitis Control Tool (ADCT) - Sleep quality NRS - Skin Pain NRS - Skin Sensitivity NRS - Skin Burning NRS	• Raw data and change from baseline; ie, absolute and percent changes, will be summarized with descriptive statistics (such as mean, median, SD, minimum, maximum, and 90% confidence interval) for AD participants based on the mITT population • Profiles for baseline to Week 17, and baseline to Week 21 time points will be generated for individual values: eg, spaghetti plot and boxplot, and patients' group means
• Proportion of AD participants reaching pruritus NRS ≥4 point improvement from baseline at Weeks 3, 5, 9, 17 and 21	• Number and percentage of AD participants reaching pruritus NRS ≥4 point improvement from baseline will be reported by time points based on the mITT population • Barplot over time of proportion of AD participants reaching pruritus NRS ≥4 point improvement from baseline will be produced.

Endpoint	Statistical analysis methods
Exploratory	
• Nanostring-Digital Spatial Profiling (N-DSP) for epidermal proteins and RNA changes from baseline in lesional skin on Weeks 3, 17, and 21	• Data will be summarized with descriptive statistics. Univariate analysis on raw data and changes from baseline for each parameter and multivariate unsupervised analysis (eg hierarchical clustering) will be performed as appropriate based on the mITT population
• Neuromarkers changes from baseline on Weeks 3, 17, and 21 in lesional skin (detected by immunohistochemistry, RNA in situ hybridization and/or RT-qPCR): - NGF - NK-1R - MRGPRX1/2/4 - TRPV1/A1 - SEMA3A - integrin alpha 6 - periostin - ANO1 - NTRK1 - NRTN - IL-4 - IL-13 - IL-31 - Mast celle, basophils, eosinophils, keratinocytes, macrophages and lymphocytes	• Data will be summarized with descriptive statistics. Univariate analysis on raw data and changes from baseline for each parameter and multivariate unsupervised analysis (eg hierarchical clustering) will be performed as appropriate based on the mITT population
• Neuronal architecture in lesional skin biopsies from AD patients and skin biopsies from healthy controls at baseline • Neuromarkers in lesional skin biopsies from AD patients and skin biopsies from healthy controls at baseline	• Descriptive statistics and plots will be produced for AD participants and healthy participants at baseline based on the mITT population
• Neuronal architecture in lesional and non-lesional skin biopsies from AD patients at baseline • Neuromarkers in lesional and non-lesional skin biopsies from AD patients at baseline	• Descriptive statistics and plots will be produced for lesional and non-lesional skin biopsies from AD participants at baseline based on the mITT population
• Neuronal architecture, Nanostring derived parameters and neuromarkers changes from baseline and clinical assessments changes from baseline	• Scatterplot to visualize the form of the relationship between changes from baseline will be produced for AD participants at specific timepoints, based on the mITT population • Pearson or Spearman's rank correlation coefficients and p-values will be reported at each defined time points based on the mITT population • A heatmap of the change from baseline of some key biomarkers could be used to have an overall representation of the evolution of those biomarkers over time in AD participants

Endpoint	Statistical analysis methods
	• As an exploratory analysis repeated measures correlation method might be used to assess the overall correlations overtime (20)

Abbreviations: AD: atopic dermatitis; mITT: modified intent-to-treat; SD: standard deviation.

9.4.8 Safety analyses

The safety evaluation will be based on the review of vital signs parameters and reported AEs. The safety analysis will be conducted according to the Sponsor's document "Analysis and reporting of safety data from Clinical Trials through the CSR" (BTD-009536).

All the safety analyses will be performed using the safety population. When applicable, results will be by groups and overall.

9.4.8.1 Adverse events

9.4.8.1.1 Definitions

Adverse events will be coded to a "Preferred Term (PT)" and "High Level Group Term (HLGT)", "High Level Term (HLT)" and primary "System Organ Class (SOC)" using the Medical Dictionary for Regulatory Activities (MedDRA, version currently in use by the Sponsor at the time of database lock).

For AD participants' group, they will be classified into predefined standard categories according to chronological criteria:

- Pre-treatment AEs: AEs that occurred, worsened or became serious during the pre-treatment period defined as the time between informed consent signature and the first IMP administration.
- Treatment-emergent AEs (TEAEs): AEs that occurred, worsened or became serious during the TEAE period defined as the time from the first IMP administration up to the EoT Visit (EoT included).
- Post-TEAEs: AEs that occurred, worsened or became serious during the post-TEAE period defined as the time starting after the TEAE period (including the follow-up period).

Treatment-emergent AEs will be assigned to the treatment received at the time of the AE onset.

If the onset date (or time) of an AE (occurrence, worsening or becoming serious) is incomplete or missing, then the AE will be considered as a TEAE unless a partial date (or time) shows it as a pre- or post-treatment event.

For all healthy participants, safety data will be considered as part of a single period starting with the signature of the informed consent and ending with the EoS Visit (EoS included).

All AEs reported in the study will be listed, sorted by participant, onset date and time.

9.4.8.1.2 Treatment-emergent adverse events

The following TEAEs summaries will be provided for the patient's group of the safety population:

Overview of TEAEs: number and percentage of subjects with any TEAE, any serious TEAE, any TEAE leading to death (if any occurred), any TEAE leading to permanent treatment discontinuation, and any TEAE of special interest.

- Summary of TEAEs by primary SOC and PT:
  - Number and percentage of patients with at least 1 TEAE;
  - Number of occurrences of TEAEs.

Patients presenting TEAEs will be listed sorted by primary SOC and PT. By definition, no TEAEs summary will be displayed for healthy participants.

AEs that occur outside the treatment-emergent period or in healthy participants will be summarized separately.

9.4.8.1.3 Deaths, serious, and other significant adverse events

Any deaths, serious and other significant AEs will be listed.

9.4.8.1.4 Adverse events leading to treatment discontinuation

Any AEs leading to permanent treatment discontinuation will be listed.

9.4.8.1.5 Adverse events of special interest (AESI)

Number (%) of subjects experiencing treatment-emergent AESI will be presented by AESI category and PT, sorted by decreasing incidence of PT within each AESI category.

9.4.8.2 Vital signs

For AD participants, heart rate, systolic and diastolic blood pressures (SBP and DBP), and body temperature will be analyzed as raw parameter value and change from baseline.

Body weight will be analyzed as raw parameter value. BMI will be analyzed as raw parameter value.

Baseline definition

The values to be used as baselines will be the Day 1 (Visit 2) predose assessment. If any of the scheduled baseline tests are repeated for any participant, the last rechecked values will be considered as baselines, provided, for patients, they were done before the IMP administration, and in the same condition.

Abnormalities analyses

For all vital sign parameters, analysis will be performed using all post-baseline assessments done during the TEAE period/safety period, including all unplanned and rechecked values. 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.

Potentially clinically significant abnormality (PCSA) Listings

A listing of individual data from participants with post-baseline PCSAs will be provided; values will be flagged when reaching the PCSA criteria.

9.4.8.3 Physical examination

Participants with at least 1 clinically significant abnormality in physical examination will be summarized and listed by treatment group.

9.5 INTERIM ANALYSES

One or more interim analyses may be performed in case of unexpected safety concerns and/or for internal decision making. As it is an open-label study with no predefined hypothesis testing there is no issue regarding blinding or multiplicity adjustment. The outcome of this interim analysis may lead to early termination of the trial, continuation without any changes, or continuation with changes.

9.6 DATA MONITORING COMMITTEE (DMC) OR OTHER REVIEW BOARD

No DMC or other review board is planned for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH-GCP Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR]).
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
    - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The ICF contains additional separate sections that addresses the use for optional exploratory and future research of participants' data and/or samples of the research substudy (remaining mandatory ones or new extra samples collected for optional research, see Section 8.8). The Investigator or authorized designee will explain to each participant the objectives of the research substudy and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

The ICF will contain a separate section that addresses the use of remaining mandatory samples or new extra samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate consent will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate consent.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR.

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on afro American population for the FDA).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data are intended to be used for the whole drug development program from collection to reimbursement.

10.1.5 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations)
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.9 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- Clinical laboratory safety tests will not be performed during the study.

  However, tests may be performed at any time during the study including screening as determined necessary by the Investigator or required by local regulations.

- Pregnancy testing and test for post menopause

  Refer to Section 5.1 (Inclusion Criteria) for screening pregnancy criteria.
  For details of timing of recommended pregnancy testing see SoA (Section 1.3).

Table 5 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only). • Highly sensitive human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential). • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).

Abbreviations: eCRF=electronic case report form; hCG: human chorionic gonadotropin; HBaAg: hepatitis B surface antigen; HIV: human immunodeficiency virus.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - 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.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc), or convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse.
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN (optional).
  - 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.

10.3.3 Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.

SAE reporting to via paper CRF (if the electronic system is unavailable)

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high 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, confirmation with >1 FSH measurement (>40 IU/L or mIU/mL) is required.
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal 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.

10.4.2 Contraception guidance

Recommended contraceptive methods are listed below in Table 6.

Table 6 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation - oral - injectable
Highly effective methods that are user independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation - 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 and less than 1 year after vasectomy, additional highly effective method 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 treatment. 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 participant.*

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 participants participating in clinical studies.

10.4.3 Collection of pregnancy information

Male AD participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive dupilumab.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
  The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female AD participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.5.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention

10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA or RNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA/RNA analysis from study participants consenting to participate in the research substudy (Section 8.7). Also, leftover skin biopsies or related material will be included in the research substudy.
- In addition to the planned RT-qPCR, ISH and N-DSP analyses of skin biopsy derived RNA described in Section 8.7, biopsy and blood samples from participants consenting to future research and from which DNA/RNA could be extracted and analyzed will be used for research as described in Section 8.7. The tissue and any isolated DNA/RNA thereof may also be used to develop tests/assays including diagnostic tests related to dupilumab and AD or related Type 2 immune diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.

- DNA and RNA samples may be used for genetic, transcriptomic and/or expression analysis. This analysis may include standard targeted methods, such as qPCR genotyping, RT-qPCR, or microarrays, as well as DNA or RNA whole genome, exome or transcriptome sequencing. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to dupilumab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA/RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on dupilumab or Type 2 immune diseases continues but no longer than 15 years or other period as per local requirements.

10.6 APPENDIX 6: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.7 APPENDIX 7: ABBREVIATIONS

AD:	atopic dermatitis
ADCT:	Atopic Dermatitis Control Tool
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
BMI:	body mass index
CGRP:	calcitonin gene-related peptide
ClinRO:	clinician reported outcomes
COPD:	chronic obstructive pulmonary disease
COVID-19:	Coronavirus Disease 2019
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSR:	clinical study report
DLQI:	Dermatology Life Quality Index
DTP:	Direct to Patient
EASI:	Eczema and severity index
eCRF:	electronic case report form
EoE:	eosinophilic esophagitis
EoS:	end of study
EoT:	end of treatment
EU:	European Union
GCP:	Good Clinical Practice

HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
IB:	Investigator's Brochure
ICF:	informed consent form
IGA:	Investigator Global Assessment
IgE:	immunoglobulin E
IHC:	immunohistochemistry
IL:	interleukin
IL-4Ra:	interleukin-4 receptor alpha
IMP:	investigational medicinal product
ISH:	in situ hybridization
ISR:	injection site reaction
ITT:	intent-to-treat
MedDRA:	Medical Dictionary for Regulatory Activities
NBF:	neutral buffered formalin
N-DSP:	Nanostring-Digital Spatial Profiling
NRS:	numeric rating scale
PACAP:	pituitary adenylate cyclase–activating polypeptide
PCSA:	potentially clinically significant abnormality
PFA:	paraformaldehyde
PGP9.5:	protein gene product 9.5
PK:	pharmacokinetics
PN:	prurigo nodularis
POEM:	Patient Oriented Eczema Measure
PRO:	patient-reported outcome
PROMIS:	Patient-Reported Outcomes Measurement Information
PT:	preferred term
Q2W:	every 2 weeks
QoL:	quality of life
RT-qPCR:	reverse transcription quantitative polymerase chain reaction
SAE:	serious adverse event
SC:	Subcutaneous
SCORAD:	Scoring Atopic Dermatitis
SoA:	schedule of activity
SOC:	system organ class
TB:	tuberculosis
TCS:	topical corticosteroids
TEAE:	treatment-emergent adverse events
Th2:	T helper cell 2
TSLP:	thymic stromal lymphopoietin
US:	United States
VIP:	vasoactive intestinal peptide

10.8 APPENDIX 8: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located before the Table of Contents (TOC).

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