AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**A randomized double-blind placebo-controlled study evaluating the effect of dupilumab on sleep in adult patients with moderate to severe atopic dermatitis**
Protocol number:	**LPS15497**
Amendment number:	**02**
Compound number (INN/Trademark):	**Dupilumab**
Short title:	**SAR231893-LPS15497- "Dupilumab effect on Sleep in AD patients"-DUPISTAD**
Sponsor name:	
Legal registered address:	

Monitoring Team's Representative Name and Contact Information

Regulatory agency identifying number(s):

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IND number:	107969
WHO number:	U1111-1223-4147
NCT number:	NCT04033367

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 02	All	07 April 2020, version 1 (electronic 4.0)
Amended Clinical Trial protocol 01	All	10 October 2019, version 1 (electronic 1.0)
Original Protocol		03 April 2019, version 2 (electronic 3.0)

Amended protocol [02] (07 April 2020)

This amended protocol (amendment 02) is considered to be substantial 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.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment incorporates few changes in the inclusion/exclusion criteria and in the timing of Patient Reported Outcomes (PROs) assessments, as well as a few minor changes summarized below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	NCT number and WHO number have been added	To complete the protocol identification information
1.3 Schedule of Activities (SoA)	SoA: the assessment of the Epworth Sleepiness Scale (ESS) is deleted at weeks 1, 2, 8, 16 and 20.	Less frequent assessments to reduce patients' burden
3 Table 1-Objectives and endpoints-Exploratory endpoints	Section 3: change from baseline in ESS will be assessed at weeks 4 and 12.	
1.3 Schedule of Activities	SoA: the assessment of the Hospital Anxiety and Depression Scale (HADS) is deleted at weeks 1, 2, 8, 16 and 20.	Less frequent assessments to reduce patients' burden, and as it may take more time to observe an improvement for this scale.
3 Table 1-Objectives and endpoints-Exploratory endpoints	Section 3: change from baseline in HADS will be assessed at weeks 4 and 12.	
1.3 Schedule of Activities	The assessment of the Patient Oriented Eczema Measure (POEM) is deleted at weeks 1, 2, 8, 16 and 20.	Less frequent assessments to reduce patients' burden

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	The assessment of the Dermatology Life Quality Index (DLQI) is deleted at weeks 1, 2, 8, 16 and 20.	Less frequent assessments to reduce patients' burden, and as it may take more time to observe an improvement for this scale.
1.3 Schedule of Activities 3 Table 1-Objectives and endpoints-Exploratory endpoints	SoA: the assessment of the Work productivity and activity impairment – Atopic Dermatitis version (WPAI-AD) is deleted at weeks 1, 2, 16 and 20. Section 3: change from baseline in WPAI-AD associated questions will be assessed at weeks 4, 8 and 12.	Less frequent assessments to reduce patients' burden
1.3 Schedule of Activities 8.1.1.5 Polysomnography (PSG) sub-study	There will be no analysis of scratching time and scratching index	Video recording (used to assist in scoring sleep studies and reveal any abnormal behaviors during the night) has a low resolution, not allowing for a proper analysis of scratching. Moreover, the PSG sub-study objective is to assess sleep-related parameters, and not to conduct a scratching analysis. This was included by error in the protocol
1.3 Schedule of activities	"Sick leave" deleted in the procedure "Assess missed school/work days"	Minor edit, to harmonize wording in the SoA with the questionnaire on missed school/work days"
1.3 Schedule of activities - foot note d 5.1 Inclusion criteria 8.1.2.1 Sleep Quality Numerical Rating Scale (NRS) 8.1.2.3 Peak pruritus NRS 10.10 - Appendix 10 PSG sub-study	For patients participating in the PSG sub-study, the sleep quality NRS and the peak pruritus NRS will be completed for 5 days, from Day -7 to Day -3 prior to baseline. Inclusion criteria 7 and 8 have been updated accordingly, and the mean of the 5-day recording will be calculated to check if these inclusion criteria are met. Sections 8.1.2.1 and 8.1.2.3 have been updated accordingly. Appendix 10: the following instruction was added: "Before any PSG procedures, the site should calculate the mean of the sleep quality NRS and the mean of the peak pruritus NRS completed for 5 days by the patients, to confirm that inclusion criteria 7 and 8 are met".	To confirm patient's eligibility before doing any PSG procedures, ie to check that inclusion criteria 7 and 8 are met before processing with the 2 PSG nights recording at baseline.
3 Table 1-Objectives and endpoints-Exploratory endpoints	The change from baseline in the Asthma Control Questionnaire-5 (ACQ-5) and in the Allergic Rhinitis-Visual Analog Scale (AR-VAS) will be assessed at week 12. There is no assessment of the change from baseline to weeks 1, 2, 4 and 8.	Minor edit, to correct a typo in Table 1, as there is no assessment of the ACQ-5 and AR-VAS at weeks 1, 2, 4 and 8, as indicated in the SoA.

Section # and Name	Description of Change	Brief Rationale
	"From baseline" was added for the analysis of the exploratory endpoint: "Missed school/work days from baseline to week 12"	Minor edit, to correct an omission in the wording of this endpoint
4.1 Overall design 8.1.1.5 PSG sub-study	Reference to a separate Informed Consent Form (ICF) for patients participating in the PSG sub-study is deleted	Minor edit, to correct an error in the protocol: there is a separate section in the global ICF for the PSG sub-study, but no separate ICF.
5.1 Inclusion criteria	Inclusion criterion 02 "Participants with chronic AD diagnosed by a physician at least 3 years before the screening visit" is changed to: "Participants with chronic AD that has been documented for at least 2 years before the screening visit"	To facilitate recruitment
5.1 Inclusion criteria	Inclusion criterion 04 "Eczema Area Severity Index (EASI) score ≥16 at screening and baseline visits" is changed to: "Eczema Area Severity Index (EASI) score ≥12 at screening and baseline visits"	To facilitate recruitment
5.2 Exclusion criteria	Exclusion criterion 14: "Patients taking sedative anxiolytic or hypnotic treatments other than melatonin within 3 months before randomization" is changed to: "Patients taking sedative anxiolytic or hypnotic treatments other than melatonin on a regular basis within 3 months before randomization. Occasional use (ie, no more than twice a week) is allowed, except within 2 weeks before randomization"	To allow for some flexibility, and as these drugs should have no impact on sleep if used occasionally (except within the 2 weeks preceding baseline)
5.2 Exclusion criteria	Exclusion criterion 15: "Sedative" was added in the note below: "Note: Patients taking systemic sedative antihistamines ≤5 days per week must be on stable regimens for at least 1 month before randomization, and maintain the same regimen throughout the study"	Minor edit, to correct an omission in this sentence.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	The wash-out period is now defined before baseline visit, instead of before screening visit, for exclusion criteria 17 (systemic cyclosporine A, systemic corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, janus kinase inhibitor, phototherapy), 18 (cell-depleting agents including but not limited to rituximab and other biologics) and 19 (investigational agents).	To allow for some flexibility and in accordance with Phase 3 pivotal studies conducted with Dupixent® in AD.
6.1 Study intervention(s) administered	The text: "To train patients how to prepare and inject IMP, the Investigator will first train the patient at an on-site visit during the treatment period. At this visit, the Investigator will perform the first of the 2 injections. The patient will perform the second injection under the supervision of the investigator or delegate. This training must be documented in the patient's study file. At subsequent study visits, patients or their caregivers will be trained to self-inject IMP, study until they are proficient and feel comfortable to self-inject the drug at home for certain intervals per Section 1.3." Is replaced by: "At on-site study visit(s) during the treatment period, patients or their caregivers will be trained by the investigator or delegate on how to prepare and self-inject/inject the IMP, until they are proficient and feel comfortable to self-inject/inject the IMP at home for certain intervals per Section 1.3. This training must be documented in the patient's study file. At baseline visit, the Investigator or delegate will perform the first of the 2 injections, and will propose to the patient or his/her caregiver to perform the second injection under the supervision of the investigator or delegate. If a patient or caregiver does not feel comfortable to self-inject/inject the IMP, all injections can be done on-site or, as an alternative, they can be done by a healthcare professional (nurse) at patients' home, after an appropriate and documented training."	To give some flexibility for IMP injections, as some patients do not feel comfortable to self-inject the IMP.

Section # and Name	Description of Change	Brief Rationale
6.5.1 Prohibited medications and procedures	The sentence: "Treatment with following concomitant medications is prohibited and restricted during the study, from screening until the end of the study visit" is changed to: "Treatment with following concomitant medications is prohibited until the end of the study". The criterion about forbidden systemic sedative antihistamines was simplified as follows: "Patients taking systemic sedative antihistamines more than 5 days per week"	For clarification, and to correct inconsistencies between section 6.5.1 and section 5.2 exclusion criteria.
6.5.2 Permitted medications	It is clarified that systemic non-sedative antihistamines are allowed during the study	Added in the protocol for clarification, as these medications do not interfere with sleep.
8.1.2.12 Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis	"Version 2.0" has been deleted in the title of this section for the WPAI-AD	As different versions are used, depending on the country
8.2.1 Vital signs	"Blood pressure and heart rate" deleted in the sentence "Vital signs (blood pressure and heart rate) will be taken at screening and …"	Minor edit, to correct a typo in the protocol, as vital signs include blood pressure, heart rate, respiratory rate and body temperature.
10.1.3 Informed consent process	The below sentence is deleted: "The ICF will contain a separate section that addresses the use of remaining samples for optional exploratory research"	Minor edit, to correct an error in the protocol: there are no lab samples collected for this study; therefore, this statement is not applicable
10.7 Appendix 7 Abbreviations	The terms "DTP (Direct To Patient)" and "TCI (Topical Calcineurin Inhibitor)" were added to the list of abbreviations	For completeness
10.8 Actigraphy	Details about questions included in the AD sleep diary are deleted, and a hyperlink is added to the AD sleep diary displayed in Appendix 9 Section 10.9. Details on how to process actigraphy data and send them to the Reading Center are deleted, and a reference to the Site Coordinator Manual is added.	For consistency reasons, and to use only one document as reference
10.9 - Appendix 9 Clinician-reported outcome-EASI	Previous scale is replaced by the one actually used in the study	The scale actually used in the study contains the correct instruction for rating the severity of erythema, edema/ papulation, excoriation, lichenification, ie, it mentions that half-points may be used, except 0.5

Section # and Name	Description of Change	Brief Rationale
10.10 - Appendix 10 PSG sub-study	-The below sentence: "The sleep center staff will document all caffeine, tobacco, alcohol, non-prescription and over the counter medications taken since awakening" is changed to: "The sleep center staff will document all caffeine, tobacco, alcohol, and prescription or over the counter medications taken since awakening". -Timelines for sending the data to the central reviewer PSG site have been changed from 3 business days to 2 business days	-To correct a typo in this sentence - For logistical reasons, to ensure a shorter assessment of data by the central reviewer PSG site

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections or formatting issues fixed) were implemented throughout the protocol.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A randomized double-blind placebo-controlled study evaluating the effect of dupilumab on sleep in adult patients with moderate to severe atopic dermatitis

Short title: SAR231893-LPS15497- "Dupilumab effect on Sleep in AD patients"- DUPISTAD

Rationale:

This study is designed to provide further evidence of the effect of dupilumab on ameliorating sleep disturbance in patients with moderate to severe atopic dermatitis (AD). Sleep disturbance represents one of the prominent symptoms of AD, and was previously shown to improve with dupilumab. This study assesses the effect of dupilumab on sleep disturbance using dedicated sleep outcome measures, in a prospective, placebo-controlled, double-blind design.

Objectives and endpoints

Note that only the primary and key secondary objectives/endpoints are listed below. A complete list of objectives and endpoints including exploratory endpoints can be found in Section 3 of the protocol.

Objectives	Supporting Endpoints
Primary	
• To evaluate the effect of dupilumab on sleep quality in adult patients with moderate to severe atopic dermatitis (AD).	• Percentage change from baseline to week 12 in sleep quality numerical rating scale (NRS).
Secondary	
• To evaluate the effect of dupilumab on objective and subjective quantitative sleep parameters, AD related outcomes, and daytime consequences of sleep deprivation.	• Secondary Endpoints • Change from baseline to week 12 in sleep efficiency (SE) based on actigraphy data. • Change from baseline to week 12 in total sleep time (TST) based on actigraphy data. • Change from baseline to week 12 in wake after sleep onset (WASO) based on actigraphy data. • Change from baseline to week 12 in sleep onset latency (SOL) based on actigraphy data. • Percent change from baseline to week 12 in Pruritus NRS. • Change from baseline to week 12 in SCORing Atopic Dermatitis (SCORAD) total score.

	• Change from baseline to week 12 in SCORAD sleep VAS. • Proportion of patients with EASI50 (reduction of EASI score by ≥50% from baseline) at week 12. • Proportion of patients with, EASI75 (reduction of EASI score by ≥75% from baseline) at week 12. • Change from baseline to week 12 in Patient Oriented Eczema Measure (POEM) total score. • Change from baseline to week 12 in Dermatology Life Quality Index (DLQI) total score. • Change from baseline to week 12 in PROMIS Sleep Related Impairment SF8a Total Score.
• To continue to assess the safety and tolerability of dupilumab throughout the study.	• Incidence of adverse events through week 12. • Incidence of adverse events through week 24.

Overall design:

This is a Phase IV, prospective, randomized, multinational study, with a 12-week double-blind placebo-controlled period, followed by a 12-week open label extension to evaluate the effect of dupilumab on sleep in adult patients with moderate to severe AD.

Number of participants:

Approximately 201 participants will be randomly assigned to study intervention in a 2:1 dupilumab to placebo ratio from multiple sites globally such that at least 150 evaluable participants (100 in the active group and 50 in placebo) complete the double-blind portion (to week 12) of the study.

Intervention groups and duration:

The study will comprise of:

- Screening period 1 (Day -28 to Day -8).
- Screening period 2 (Pre-baseline assessments): patients eligible to continue, will complete assessments specified in schedule of activities (SoA) from Day -7 to Day -1 (right before Day 1). If preferred by the patient and the investigator for logistical reasons, screening can be done during a single on-site visit. In that case, all procedures planned at screening 1 and screening 2 should be done during this single screening visit. Importantly, this single screening visit will have to be done at least 7 days before the baseline visit, as patients should wear the actigraph and complete the diary for 7 days before baseline.
- Baseline/Randomization/Administration of first dose (Day 1).
- 12-week double-blind placebo-controlled period: patients will be randomized to receive dupilumab or placebo.

- 12-week open-label extension period: following completion of double-blind period, patients randomized to dupilumab will continue to receive active treatment in the open-label period, whereas patients randomized to placebo will receive active treatment with dupilumab.

The maximum study duration per participant will be up to 28 weeks.

Polysomnography (PSG) sub-study: Of the 201 participants, approximately 30 patients total (approximately 20 dupilumab and 10 placebo patients) will participate in a PSG sub-study at selected US sites. Each patient who participates in this sub-study will have a total of 3 overnight PSGs: at baseline, 2 (preferably) consecutive overnight PSGs to control for "first night effect" (night of Day -2) and collect baseline data (night of Day -1; which will serve as baseline assessments); then 1 overnight PSG at week 12. The assessment procedure is provided in Section 10.10.

Study interventions

Investigational medicinal products

- Formulation:
  - Dupilumab: 150 mg/mL in pre-filled syringe to deliver 300 mg in 2 mL,
  - Placebo: Pre-filled syringe to deliver 2 mL of vehicle solution, containing all ingredients except the protein (dupilumab), visually indistinguishable from the dupilumab syringe.
- Route of administration: Subcutaneous
- Dose regimen:
  - Patients initially assigned to dupilumab will receive 600 mg (2 x 300 mg dupilumab injections) on Day 1 (ie, the loading dose), followed by 1 dupilumab injection of 300 mg every 2 weeks (Q2W) until week 10, then 1 dupilumab +1 placebo injection at week 12 (to protect the blind while placebo patients receive their loading dose), followed by 1 dupilumab injection Q2W, with a last injection at week 22.
  - Placebo patients will receive 2 x 2 mL placebo injections on Day 1, then 1 placebo injection Q2W until week 10, and then 2 x 300 mg dupilumab injections at week 12 (ie, the loading dose), followed by 1 dupilumab injection Q2W, with a last injection at week 22.

Post-trial access to study medication

After the study is completed, patients will not be provided any further study medication as part of this protocol.

Statistical considerations:

- **Primary analysis:**

  The percent change from baseline to week 12 in sleep quality NRS will be analyzed using a mixed effect model with repeated measures (MMRM) with treatment, baseline value, randomization stratum, visit, treatment by visit interaction, and baseline value by visit interaction terms (all as fixed effects) in the model.

- **Analysis of secondary endpoints:**

  For analysis of secondary continuous endpoints, a similar approach will be used as above. Each endpoint will be analyzed using a MMRM with treatment, corresponding baseline value, randomization stratum, visit, treatment by visit interaction, and baseline value by visit interaction terms (all as fixed effects) in the model.

  Endpoints comparing proportion of patients meeting certain criteria at a specific visit will be analyzed via the Cochran Mantel-Haenszel test adjusted by the randomization stratum.

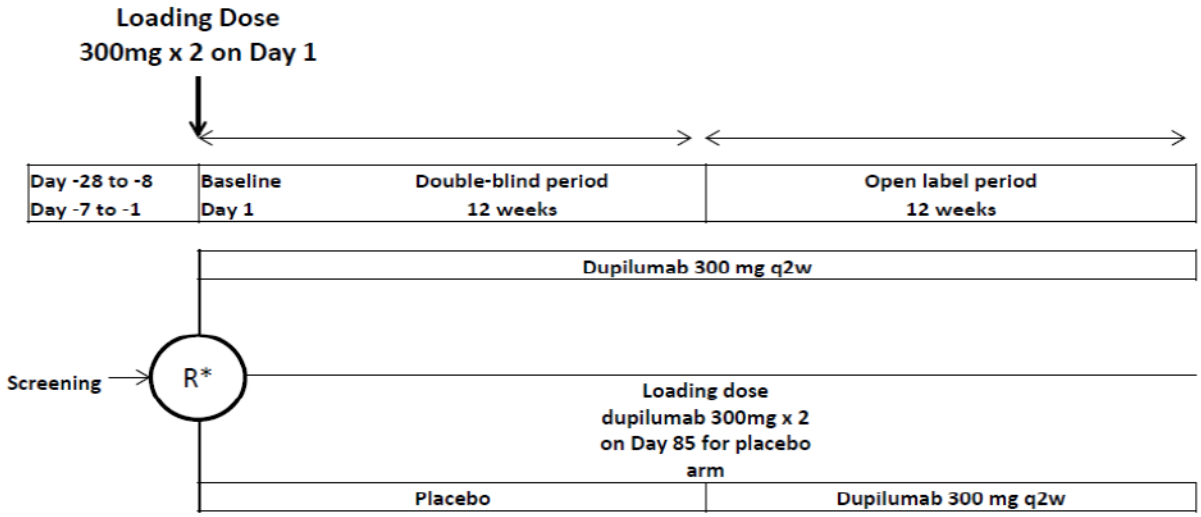
- **Multiplicity Considerations:**

  Multiplicity adjustments will be considered to protect the Type I error at 0.05 level (2-sided), due to testing primary and multiple secondary endpoints, as described in Section 8.1.4.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: q2w=every 2 weeks

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Procedure													
Visit (V)	Screen-ing 1[g]	Screen-ing 2[g]	Baseline V1	V2	V3	V4	V5	Primary End point Visit V6	V7	V8	End of Study/ Early discontin-uation V9[h]	UnSch Visit	Notes
Week (W)			W0	W1	W2	W4	W8	W12	W16	W20	W24		
Day (D) Visit window (±d)	D (-28 to -8)	D (-7 to -1)	D1	D8 ±3d	D15 ±3d	D29 ±3d	D57 ±3d	D85 ±3d	D113 ±3d	D141 ±3d	D169 ±3d		
Enrollment Screening/Baseline:													
Inclusion and exclusion criteria	X		X										
Informed consent	X												
Demography	X												
Concurrent illness	X		X										
IVRS call	X		X		X	X	X	X	X	X	X		
Study Treatment/Concomitant Medication:													
Study drug dispensation			X[a]		X[b]	X	X	X[c]	X	X			
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy:													
Physician Assessments:													

Study Procedure													
Visit (V)	**Screen-ing 1[g]**	**Screen-ing 2[g]**	**Baseline V1**	**V2**	**V3**	**V4**	**V5**	**Primary End point Visit V6**	**V7**	**V8**	**End of Study/ Early discontin-uation V9[h]**	**UnSch Visit**	**Notes**
Week (W)			**W0**	**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**		
Day (D) **Visit window (±d)**	**D (-28 to -8)**	**D (-7 to -1)**	**D1**	**D8 ±3d**	**D15 ±3d**	**D29 ±3d**	**D57 ±3d**	**D85 ±3d**	**D113 ±3d**	**D141 ±3d**	**D169 ±3d**		
IGA and BSA (for eligibility purpose only)	X		X										
EASI	X		X	X	X	X	X	X	X	X	X	X	
SCORAD	X		X	X	X	X	X	X	X	X	X	X	
Patient Assessments (Daily including week preceding baseline visit):													
Sleep Quality NRS[d]		X	X	X	X	X	X	X	X	X	X	X	
Sleep Diary[d]		X	X	X	X	X	X	X	X	X	X	X	
Peak pruritus NRS, Skin pain NRS, Skin sensitivity to touch, Skin burn NRS[d]		X	X	X	X	X	X	X	X	X	X	X	
Actigraphy[d]		X	X	X	X	X	X	X	X	X	X	X	
Patient Assessment (at clinic):													
PROMIS Sleep Related Impairment SF 8a			X	X	X	X	X	X	X	X	X	X	
Epworth Sleepiness Scale (ESS)			X			X		X			X	X	

Study Procedure													
Visit (V)	**Screen-ing 1[g]**	**Screen-ing 2[g]**	**Baseline V1**	**V2**	**V3**	**V4**	**V5**	**Primary End point Visit V6**	**V7**	**V8**	**End of Study/ Early discontin-uation V9[h]**	**UnSch Visit**	**Notes**
Week (W)			**W0**	**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**		
Day (D) **Visit window (±d)**	**D (-28 to -8)**	**D (-7 to -1)**	**D1**	**D8 ±3d**	**D15 ±3d**	**D29 ±3d**	**D57 ±3d**	**D85 ±3d**	**D113 ±3d**	**D141 ±3d**	**D169 ±3d**		
POEM			X			X		X			X	X	
DLQI			X			X		X			X	X	
HADS			X			X		X			X	X	
ACQ-5, AR-VAS			X					X			X	X	
WPAI-AD			X			X	X	X			X	X	
Assess missed school/work days			X			X	X	X	X	X	X	X	
Center assisted Assessment:													
Psychomotor Vigilance Test (PVT)	X		X					X			X	X	
Neurocognitive test (Automated Neuropsychological Assessment Metrics-ANAM)	X		X					X			X	X	
Polysomnography (sub-study, select sites)[e]			X[e]					X					
Skin Photography[f]			X	X	X	X	X	X	X	X	X	X	

Study Procedure													
Visit (V)	Screening 1[g]	Screening 2[g]	Baseline V1	V2	V3	V4	V5	Primary End point Visit V6	V7	V8	End of Study/ Early discontinuation V9[h]	UnSch Visit	Notes
Week (W)			W0	W1	W2	W4	W8	W12	W16	W20	W24		
Day (D) Visit window (±d)	D (-28 to -8)	D (-7 to -1)	D1	D8 ±3d	D15 ±3d	D29 ±3d	D57 ±3d	D85 ±3d	D113 ±3d	D141 ±3d	D169 ±3d		
Sleep diary uploading			X	X	X	X	X	X	X	X	X	X	
Safety:													
Weight	X										X		
Height	X												
Vital signs	X		X	X	X	X	X	X	X	X	X	X	
Physical examination			X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Testing:													
Urine Pregnancy Test (WOCBP only)	X		X			X	X	X	X	X	X	X	

Abbreviations: ACQ-5 = asthma control questionnaire; AR-VAS = Allergic Rhinitis-visual analog scale; BSA = body surface area; D = day; DC = discontinuation; DLQI = dermatology life quality index; EASI = eczema area and severity index; HADS = hospital anxiety and depression scale; IGA = Investigator's global assessment; NRS = numerical rating scale; POEM = patient oriented eczema measure; PROMIS = patient-reported outcomes measurement information system; SCORAD = SCORing atopic dermatitis; UnSch = Unscheduled; V = visit; WOCBP = women of childbearing potential; WPAI-AD = work productivity and activity impairment – Atopic Dermatitis version; w = week

a Loading dose dupilumab arm 600 mg (300 mg x 2 ie, 2 syringes); 2 placebo syringes for the placebo arm.

b Regular dose dupilumab arm 300 mg (1 syringe) and 1 syringe for placebo arm, for q2w injections at sites and for home injections.

c In order to protect the blind prior to this point to reduce bias in the open label period, at the beginning of open label (week 12), for loading dose, dupilumab arm will have 1 x 300 mg syringe and 1 placebo syringe; placebo arm will need to remain 2 syringes, 300 mg each; then subsequent dose will be 1 syringe of 300 mg for all patients in both arms.

d For patients who do not participate to the PSG sub-study: Patients eligible to continue, except for baseline severity criteria, will complete baseline assessments from Day -7 to Day -1 (right before Day 1); daily assessment thereafter until week 4; then only the week before a clinical visit until last study visit. For patients who participate to the PSG sub-study: same procedures as for the other patients, except that the sleep quality NRS and the peak pruritus NRS will be completed for 5 days, from Day -7 to Day -3 prior to baseline.

e Each patient who participates in this sub-study will have a total of 3 overnight PSGs: at baseline time point, 2 (preferably) consecutive overnight PSGs to control for "first night effect" and collect baseline data, and 1 more at week 12.

f Not mandatory, site professional will be taking the photographs with patient's consent; Site staff will take the photos of the same lesioned areas for each visit, starting from the baseline visit. Patients will be asked to sign a separate photography informed consent at Day 1.

g If preferred by the patient and the investigator for logistical reasons, screening can be done during a single on-site visit. In that case, all procedures planned at screening 1 and screening 2 should be done during this single screening visit. Importantly, this single screening visit will have to be done at least 7 days before the baseline visit, as patients should wear the actigraph and complete the diary for 7 days before baseline.

h V9 assessments are applied to patients who prematurely discontinue the study, complete the treatment (end of treatment), and complete the study (end of study).

2 INTRODUCTION

Dupilumab is a recombinant human immunoglobulin-G4 (Ig-4) monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha (IL 4Rα) sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL 4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). These cytokines play key roles in the pathogenesis of various allergic diseases, including AD (1) and asthma (2).

Dupilumab 300 mg Q2W is approved for the treatment of adult AD in the US, EU and many other countries worldwide. Completed phase III studies (SOLO 1 R668-AD-1334, SOLO 2 R668-AD-1416, CHRONOS R668-AD-1224, and R668-AD-1424) have demonstrated the safety and efficacy of dupilumab 300 mg administered subcutaneously (SC) Q2W or every week (QW) as a monotherapy or concomitantly with topical corticosteroids (TCS) in patients with moderate to severe AD inadequately controlled with topical medications.

Atopic dermatitis is a chronic/relapsing inflammatory skin disease characterized by intense pruritus, dry skin, and eczematous lesions. An estimated 15% to 30% of children and 2% to 10% of adults are affected by AD (3). Atopic dermatitis is commonly associated with asthma and other atopic/allergic conditions, with which it shares common pathophysiological pathways. The pathophysiology of AD is influenced by genetics and environmental factors and involves a complex interplay between antigens, skin barrier defects, and immune dysregulations, in which a polarized inflammatory response induced by the marked activation of the T-helper Type 2 (Th2) cell axis plays a central role (1). Two cytokines, IL-4 and IL-13, are critical in the initiation and maintenance of the Type 2/Th2 inflammatory pathway.

Moderate-to-severe AD is an under-recognized public health concern with a high disability burden (4). In patients with moderate AD, and especially in patients with severe AD, the clinical manifestations lead to significant sleep disturbances and severe psychological and sociological sequelae, impaired quality of life (QoL) with substantial negative impact on patient's day-to-day functioning, and are associated with high socioeconomic costs.

2.1 STUDY RATIONALE

Sleep disturbance is a well-known debilitating symptom of AD, though few studies have investigated it as a primary outcome to assess the impact of this condition on patient's QoL and other important outcomes that patients suffer in their daily lives. This double-blind, placebo-controlled, prospective study will apply both objective and subjective tools to measure qualitative and quantitative sleep related outcomes and comprehensively assess dupilumab treatment effect on sleep and on the consequences of sleep deprivation including daytime sleepiness, daily function, neurocognitive and psychomotor function, productivity, and QoL in adult patients with moderate to severe AD.

2.2 BACKGROUND

Atopic dermatitis is a chronic type 2 inflammatory skin disease that is associated with heterogeneous and highly variable signs and symptoms. The symptoms of AD include cutaneous itch, pain sleep disturbance, and mental health symptoms. Atopic dermatitis patients also can suffer from comorbid infectious, autoimmune, respiratory, neuropsychiatric, and musculoskeletal disorders. Atopic dermatitis might have systemic involvement with global impact beyond the skin signs and symptoms.

Atopic dermatitis patients often exhibit a variety of psychosocial symptoms such as anxiety, frustration and embarrassment. Accordingly, they also often report lower self-esteem and self-confidence, and reduced ability to establish and manage relationships (5). Among the main goals in treating AD are reducing skin inflammation and alleviating symptoms, while improving the patients' QoL and sleep. Lack of proper sleep may cause daytime sleepiness, impaired cognition and mood changes which consequently might decrease the productivity and other important aspects of life quality (6). A review of the relevant literature pointed out the fact of high prevalence of sleep disturbance in adults with AD which can have a remarkable effect on QoL (7).

There are a number of potential risk factors for sleep disturbance in AD patients, including the itch-scratch cycle, lesional and central pain, poor sleep hygiene, circadian rhythm-induced modification of itch, and secondary effects of inflammatory cytokines on sleep regulation.

Earlier studies have shown substantially impaired quality of sleep in both childhood and adult AD, with reduced sleep overall, more regular and protracted awakening, overall decreased sleep efficiency, and increased daytime dysfunction being reported. Actigraphy and infrared video (objective measures of sleep) revealed fragmented sleep with more night-time awakenings, prolonged awakenings, lower overall sleep efficiency, increased scratch time, and restless nocturnal movement in both adults and children with AD.

The International Study of Life with Atopic Eczema performed a multicenter questionnaire-based study including 1,098 adults and discovered that patients had an average of 8.4 nights of disrupted sleep with a typical AD flare, which worked out as ~81 days per patient-year. A study of 34, 613 adults from the 2012 NHIS found that 25–33% of US adults with self-reported eczema reported fatigue, regular daytime sleepiness, and regular insomnia. Adults with self-reported eczema were also more likely to report either short or long sleep duration. Atopic dermatitis and fatigue, sleepiness, and insomnia were significant predictors of poorer overall health, number of sick days, and doctor visits, with eczema in combination with sleep symptoms associated with a greater chance of worse outcomes than either sleep symptoms or eczema alone. A study of 5, 563 adults from the National Health and Nutrition Examination Survey found that US adults with AD more commonly reported short sleep duration, trouble falling asleep, night-time awakenings, early morning awakenings, and leg jerks and leg cramps during sleep and were more likely to feel unrested, being overly sleepy during the day and feeling as if they did not get enough sleep. Sleep disturbances may have very detrimental effects in AD patients, including poor performance at school and work, impaired health-related QoL, considerable economic burden, and increased risk of psychological disorders, motor vehicle accidents, and workplace injury. Together, these studies

suggest that sleep disturbances are both very common and burdensome in AD patients and warrant interventions for their treatment and prevention (5).

Analyses of sleep related outcomes such as SCORing atopic dermatitis (SCORAD) sleep loss scores from dupilumab phase III studies (SOLO 1,2, CHRONOS, and CAFÉ) supported strong correlations between the improvement of clinical outcomes and significant sleep benefit in patients with moderate to severe AD. Additionally some other studies in AD provided promising improvement in sleep as measured by actigraphy when the disease is controlled effectively (8).

2.3 BENEFIT/RISK ASSESSMENT

Moderate-to-severe AD is a serious inflammatory skin disease with a high disability burden. Atopic dermatitis treatment is typically long-term, given that AD is a chronic systemic disease, and exacerbations of signs and symptoms (eg, flares) can be frequent, unpredictable, and disruptive. Safe and effective therapies are not currently available for a large number of AD patients whose disease cannot be adequately controlled with topical treatments or for whom topical treatments are otherwise inadvisable. Systemic immunosuppressants used in AD are associated with toxicity and long-term side effects, thus limiting their use to short courses and/or intermittent therapy, which often leads to relapse or rebound upon treatment withdrawal.

As a targeted agent, selectively inhibiting the IL-4 and IL-13 signaling, dupilumab is a novel systemic therapy for AD, demonstrating significant and clinically meaningful benefits combined with a favorable safety profile, compared to existing non-selective systemic immunosuppressants. The totality of clinical evidence, which included data from patients with moderate-to-severe AD from 11 studies, demonstrated a markedly favorable benefit/risk ratio for dupilumab 300 mg Q2W, both monotherapy up to 16 weeks or in combination with TCS up to 52 weeks. Furthermore, the placebo-controlled maintenance study (SOLO-Continue) also provided additional support for dupilumab 300 mg Q2W as long-term dose-regimen in patients with moderate-to-severe AD.

The benefits include clearance of skin AD lesions, or at least a substantial reduction of lesion extent and severity, in conjunction with relief of subjective symptoms, particularly pruritus, hallmark of AD and frequent cause of secondary symptoms such as sleep loss and associated disability. The improvements in AD signs and symptoms were paralleled by improvements in quality of life, reduced anxiety and depression scores, and improved day-to-day functioning and overall patients' well-being. These benefits occurred within 1 to 2 weeks of treatment initiation and are sustained with continued treatment.

From a safety perspective, dupilumab was generally well tolerated and the safety profile was largely comparable to placebo. The adverse drug reactions (ADRs) identified to date for dupilumab include injection site reactions, conjunctivitis, oral herpes, allergic conjunctivitis, bacterial conjunctivitis, herpes simplex, blepharitis, dry eye, eye pruritus, and eosinophilia. Except for injection site reactions, these ADRs are commonly seen in the AD patient population; they occurred with relatively low frequency with dupilumab treatment, and were generally mild and moderate, transient, and manageable. More significant serious allergic reactions were very

rare. Importantly, no increased overall infection risk was observed in patients treated with dupilumab. Furthermore, there are no important safety concerns for long-term treatment with dupilumab, which is critical for a chronic disease like AD. Since dupilumab's onset of action is rapid and clinically evident, patients and healthcare providers can easily determine if dupilumab is having the intended effect shortly after initiation of treatment, allowing for appropriate risk mitigation by discontinuing treatment in patients who do not respond to dupilumab. There is no evidence of disease rebound after discontinuation of dupilumab treatment, so treatment may be discontinued safely, taking into consideration SmPC guidance in case of systemic hypersensitivity reaction, helminth infection (until resolution of the infection) and comorbid asthma (careful monitoring).

Additional detailed information about the known and expected benefits and risks and reasonably expected adverse events (AE) of dupilumab can be found in the Investigator's Brochure (IB), Prescribing Information (PI), or Summary of Product Characteristics.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of dupilumab on sleep quality in adult patients with moderate to severe atopic dermatitis (AD)	• Percentage change from baseline to week 12 in sleep quality numerical rating scale (NRS)
Secondary	
• To evaluate the effect of dupilumab on objective and subjective quantitative sleep parameters, AD related outcomes, and daytime consequences of sleep deprivation.	• <u>Secondary Endpoints</u> • Change from baseline to week 12 in sleep efficiency (SE) based on actigraphy data • Change from baseline to week 12 in total sleep time (TST) based on actigraphy data • Change from baseline to week 12 in wake after sleep onset (WASO) based on actigraphy data • Change from baseline to week 12 in sleep onset latency (SOL) based on actigraphy data • Percent change from baseline to week 12 in Pruritus NRS • Change from baseline to week 12 in SCORing Atopic Dermatitis (SCORAD) total score • Change from baseline to week 12 in SCORAD sleep VAS • Proportion of patients with EASI50 (reduction of EASI score by ≥50% from baseline) at week 12 • Proportion of patients with, EASI75 (reduction of EASI score by ≥75% from baseline) at week 12 • Change from baseline to week 12 in Patient Oriented Eczema Measure (POEM) total score • Change from baseline to week 12 in Dermatology Life Quality Index (DLQI) total score • Change from baseline to week 12 in PROMIS Sleep Related Impairment SF8a Total Score
• To continue to assess the safety and tolerability of dupilumab throughout the study.	• Incidence of adverse events through week 12 • Incidence of adverse events through week 24

Objectives	Endpoints
Exploratory	
• To further evaluate the effect of dupilumab on objective and subjective sleep parameters, AD-related outcomes, and daytime consequences of sleep deprivation.	Exploratory Endpoints: • Percent change from baseline in sleep quality NRS to week 1, 2, 4, and 8. • Percent change from baseline in pruritus NRS to week 1, 2, 4, and 8. • Change from baseline in sleep efficiency based on actigraphy to week 1, 2, 4, and 8. • Change from baseline in WASO based on actigraphy to week 1, 2, 4, and 8. • Change from baseline in TST based on actigraphy to week 1, 2, 4, and 8. • Change from baseline in sleep latency based on actigraphy to week 1, 2, 4, and 8. • Change from baseline in SCORAD total score and sleep VAS to week 1, 2, 4, and 8. • EASI50 and EASI75 at weeks 1, 2, 4, and 8. • Change from baseline to week 12 in PSG measures of sleep efficiency, TST, WASO, and sleep latency. • Change from baseline to weeks 1, 2, 4, and 8 in PROMIS Sleep Related Impairment SF8a total score. • Change from baseline to week 1, 2, 4, 8, and 12 in skin pain NRS. • Change from baseline to week 1, 2, 4, 8, and 12 in skin sensitivity to touch NRS. • Change from baseline to week 1, 2, 4, 8, and 12 in skin burn NRS. • Change from baseline in SOL, TST, number of awakenings, WASO, sleep efficiency, and how rested to week 1, 2, 4, 8, and 12 based on sleep diary. • Change from baseline to week 4 and 12 in Epworth Sleepiness Scale (ESS). • Change from baseline to week 12 in psychomotor vigilance test (PVT). • Change from baseline to week 12 in Running Memory, Mathematical Processing and Procedural Reaction Time scores based on the neurocognitive test (Automated Neuropsychological Assessment Metrics [ANAM]). • Work productivity and activity impairment – Atopic Dermatitis version (WPAI-AD) associated questions change from baseline to weeks 4, 8, and 12. • Missed school/work days from baseline to week 12.
• To evaluate the relationships between sleep disturbance and other objective and subjective parameters associated with AD.	• Relationship between variables relating to sleep disturbances (eg, TST, WASO) and objective and subjective parameters associated with AD (eg, EASI,

Objectives	Endpoints
	SCORAD, pruritus NRS, DLQI, EASI, skin pain NRS, and skin burn NRS sensitivity to touch NRS). Exploratory Endpoints: • Change from baseline to week 12 in ACQ-5 among those who reported asthma at baseline. • Change from baseline to week 12 AR-VAS among those who reported allergic rhinitis at baseline. • Change from baseline to weeks 4 and 12 in HADS-anxiety and HADS-depression scores.
• To evaluate the effect of dupilumab in comorbid conditions.	
• To evaluate the effect of dupilumab on individual quantitative and non-sleep related endpoints associated with AD at week 24.	• Change or percent change (as used in analyses of week 12 data) from baseline to week 24 for primary and secondary endpoints. • Change or percent change (as used in analyses of week 12 data) from week 12 to week 24 for primary and secondary endpoints.

3.1 APPROPRIATENESS OF MEASUREMENTS

Appropriateness of measurements is described in Section 8.1 and Section 8.2.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a phase IV randomized, double-blind, placebo-controlled study evaluating the effect of dupilumab on sleep in adult patients with moderate to severe AD.

The study will comprise of:

- Screening Period 1 (Day -28 to -8): Patients will be evaluated according to inclusion and exclusion criteria.
- Screening Period 2 (Day -7 to -1; Pre-baseline assessments): eligible patients will complete the daily sleep, quality, daily pruritus, skin pain, skin sensitivity, and touch skin burn, sleep diary, and will wear an actigraph at night-time during the 7 days immediately preceding the Baseline visit (Day 1). If preferred by the patient and the investigator for logistical reasons, screening can be done during a single on-site visit. In that case, all procedures planned at screening 1 and screening 2 should be done during this single screening visit. Importantly, this single screening visit will have to be done at least 7 days before the baseline visit, as patients should wear the actigraph and complete the diary for 7 days before baseline.
- Baseline (Day 1): Patients who remain eligible will be randomized
- 12-week double-blind placebo-controlled period: Patients will be randomized to receive dupilumab or placebo
- 12-week open-label extension period: Following completion of double-blind period, patients randomized to dupilumab will continue to receive active treatment for open-label period, whereas patients randomized to placebo will receive active treatment with dupilumab.

The maximum study duration per participant will be 28 weeks.

Polysomnography (PSG) sub-study will be conducted at selected US sites in up to 30 patients total (up to 20 dupilumab and 10 placebo patients). Each patient who participates in this sub-study will have a total of 3 overnight PSGs: at baseline timepoint, 2 (preferably) consecutive overnight PSGs to control for "first night effect" (night of Day -2) and collect baseline data (night of Day -1); then 1 overnight PSG at week 12. Selection of patients for the PSG sub-study will be based on their proximity to participating sleep centers and availability for overnight stay.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Sleep disturbance is a well-known debilitating symptom of AD, though few studies have investigated it as a primary outcome to assess the impact of this condition on patient's QoL and other important outcomes that patients suffer in their daily lives. This double-blind prospective study will apply both objective and subjective tools to measure sleep related outcomes and comprehensively assess dupilumab treatment effect on sleep disturbance, and consequential

aspects of sleep deprivation including daytime sleepiness, daily function, neurocognitive and psychomotor function, productivity, and QoL for adult patients with AD disease.

The double-blind design intends to mitigate potential bias and placebo control is necessary to assess the net effect of active dupilumab treatment.

Placebo patients will be receiving active dupilumab at week 12; which will enhance recruitment and retaining patients in a phase IV trial where the investigational product has already been commercially available for their usage. It will also help to capture rare events such as health care resource utilization and work productivity which might take a longer time to occur.

4.3 JUSTIFICATION FOR DOSE

The dose selected in this study is the dose approved for the treatment of moderate to severe AD for Dupixent in US, EU, and all other countries that this study will be conducted.

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 the last scheduled visit shown in the SoA (Section 1.3).

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment 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:

Age

I 01. Participant must be 18 years of age or older, at the time of signing the informed consent

Type of participant and disease characteristics

I 02. Participants with chronic AD that has been documented for at least 2 years before the screening visit

I 03. Inadequate response to topical medications or otherwise candidate for systemic AD treatment

I 04. Eczema Area Severity Index (EASI) score ≥12 at screening and baseline visits

I 05. Investigator's global assessment (IGA) score ≥3 (on the 0 to 4 IGA scale) at the screening and baseline visits

I 06. ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits

I 07. Baseline pruritus NRS score for maximum itch intensity ≥3 (based on weekly average of daily scores during the 7 days immediately preceding baseline, or based on average of daily scores completed for 5 days (from Day -7 to Day -3 prior to baseline) for patients participating in the PSG sub-study; at least 4 ratings over the prior week/over the 5 days are required to calculate the average)

I 08. Baseline Sleep Quality NRS score ≤5 (based on weekly average of daily scores during the 7 days immediately preceding baseline, or based on average of daily scores completed for 5 days (from Day -7 to Day -3 prior to baseline) for patients participating in the PSG sub-study; at least 4 ratings over the prior week/over the 5 days are required to calculate the average)

I 09. Have been applying skin emolients (moisturizers) twice daily (once daily on areas receiving backgound topical medications – see I 10 below and Section 6) for at least 7 days prior to randomization

I 10. Have been applying medium-potency TCS on all active AD lesions, once daily for at least 7 days before randomization, using the standardized regimen provided in the protocol.

Note: Low-potency TCS or topical calcineurin inhibitor (TCI) may be used on areas that cannot be safely treated with medium- potency TCS (eg, face, genital, flexural areas, or areas of skin atrophy)

I 11. Willing and able to comply with all clinic visits and study-related procedures

Weight

Not applicable.

Sex

Male or female

Informed Consent

I 12. Capable of giving signed informed consent as described in Section 10.1 (Appendix 1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of adulthood is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Known hypersensitivity to Dupixent including all excipients

E 02. Evidence of drug abuse in past 2 years

E 03. Sleep disturbances not related to AD, including sleep apnea, hypersomnia, or insomnia secondary to chronic pain, uncontrolled asthma, chronic obstructive pulmonary disease, etc., as determined by the Investigator

E 04. Patients who work night shifts (ie, any work between 8 pm and 6 am)

E 05. Patients with erratic sleep habits, as determined by the Investigator

E 06. Evidence of restless leg syndrome or periodic limb movement disorder

E 07. Acute infection requiring systemic treatment within 1 week before the screening visit

Note: Patients may be rescreened no sooner than 1 week after the infection resolves, and with permission of the Sponsor's Medical Monitor

E 08. Active endoparasitic infections (helminths); suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization

E 09. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to, patients with short life expectancy, patients with uncontrolled diabetes (hemoglobin A1c [HbA1c] ≥9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), neuro-inflammatory disease, other severe endocrinological, gastrointestinal, metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc.)

E 10. Any other medical or psychological condition (including relevant laboratory abnormalities) that in opinion of investigator may present an unreasonable risk to the study patient as a result of his/her participation in clinical trial, may make patient's participation unreliable or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRFs, etc.)

E 11. Presence of skin conditions that may interfere with study assessments

E 12. Contraindications or important side effects of TCS (eg, intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the Investigator

E 13. At baseline, presence of any conditions listed as criteria for study drug discontinuation (see Section 7.1)

Prior/concomitant therapy

E 14. Patients taking sedative anxiolytic or hypnotic treatments other than melatonin on a regular basis within 3 months before randomization. Occasional use (ie, no more than twice a week) is allowed, except within 2 weeks before randomization

E 15. Patients taking systemic sedative antihistamines more than 5 days a week. Note: Patients taking systemic sedative antihistamines ≤5 days per week must be on stable regimens for at least 1 month before randomization, and maintain the same regimen throughout the study

E 16. Current treatment with antidepressants, lipophilic beta blockers, clonidine, opioids, theophylline, or other medications known to interfere with sleep and may confound the study assessments, as determined by the Investigator. Note: In most cases, chronic treatments administered regularly and at stable dosing should be acceptable. Investigators

should assess the degree to which an individual medication may cause changes in sleep pattern or sleep quality during the study, compared to the pre-baseline state

E 17. Systemic cyclosporine A (CsA), systemic corticosteroids, azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or janus kinase (JAK) inhibitors, or phototherapy within 4 weeks prior to baseline visit

E 18. Treatment with biologics as follows:

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

E 19. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to baseline

E 20. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit

E 21. Planned or anticipated use of any prohibited medications and procedures (see Section 6.5)

E 22. Treatment with live (attenuated) vaccine within 12 weeks before the screening visit

Prior/concurrent clinical study experience

E 23. Current participation in another investigational clinical study

Diagnostic assessments

E 24. Not applicable.

Other exclusions

E 25. Any other condition (medical, personal, familial, social, environmental, etc.) as assessed by the Investigator, that could significantly alter sleep parameters and confound study assessments

E 26. Planned or anticipated major surgical procedure during the patient's participation in this study

E 27. Pregnant or breast-feeding women, or were planning to become pregnant or breastfeed during the patient's participation in this study

E 28. Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control is defined as agreement to consistently practice an effective

and accepted method of contraception throughout the duration of the study and for at least 12 weeks after last dose of study drug. These include hormonal contraceptives, intrauterine device, or double barrier contraception (ie, condom + diaphragm) or a male partner with documented vasectomy. Additional requirements for acceptable contraception may apply in certain countries, based on local regulations. Investigators in these countries will be notified accordingly in a protocol clarification letter

*For females, menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone (FSH) level of ≥25 mU/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently eligible to be enrolled 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, typically once.

6 STUDY INTERVENTION

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

Study intervention name	Dupilumab	Placebo
Dosage formulation	Dupilumab 300 mg for SC administration is supplied as 150 mg/mL solution in 2.25 mL pre-filled glass syringes to deliver 300 mg in 2.0 mL	Placebo for dupilumab will be provided in identically matched glass pre-filled syringe to deliver 2 mL, which will match dupilumab 300 mg.
Unit dose strength(s)/Dosage level(s)	300 mg	Not applicable
Route of administration	Subcutaneous	Subcutaneous
Dosing instructions	Dupilumab 300 mg SC Q2W (with a 600 mg loading dose at randomization Day 1, then followed with dupilumab 300 mg SC Q2W until week 10); At week 12, dupilumab 300 mg plus 1 placebo to mask prior blinding; then followed with 300 mg SC Q2W with a last injection at week 22	Placebo SC Q2W to deliver 2 mL (with placebo loading dose at randomization Day 1, then followed with 1 placebo dose Q2W until week 10); At week 12, dupilumab 600 mg loading dose; then followed with dupilumab 300 mg SC q2w with a last injection at week 22
Packaging and labeling	Dupilumab will be supplied as 1 glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement.	Placebo will be supplied as 1 glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement.

Abbreviations: SC=subcutaneous; Q2W=every 2 weeks

INVESTIGATIONAL MEDICINAL PRODUCT(S)

Investigational medicinal product (IMP) will be administered by the Investigator/health care professional or designee following clinic procedures and blood collection. Patients should be monitored by site personnel or by caregiver[s] (if at home) for at least 30 minutes after administration of all IMP injections.

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 visits.

At on-site study visit(s) during the treatment period, patients or their caregivers will be trained by the investigator or delegate on how to prepare and self-inject/inject the IMP, until they are proficient and feel comfortable to self-inject/inject the IMP at home for certain intervals per

Section 1.3. This training must be documented in the patient's study file. At baseline visit, the Investigator or delegate will perform the first of the 2 injections, and will propose to the patient or his/her caregiver to perform the second injection under the supervision of the investigator or delegate. If a patient or caregiver does not feel comfortable to self-inject/inject the IMP, all injections can be done on-site or, as an alternative, they can be done by a healthcare professional (nurse) at patients' home, after an appropriate and documented training.

Patient or caregiver injection should only be performed in the abdomen or upper thighs. Patient should also be instructed to monitor for any reaction for at least 30 minutes (or longer per country-specific or local site-specific requirements) following injection.

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

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, 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 subject.

NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Patients will receive standardized background treatment (ie, non-investigational medical products [NIMP]) consisting of TCS as noted below. Between the protocol-scheduled on-site visits, interim visits may be required for NIMP dispensing. As an alternative to these visits, TCS may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the subject.

Starting on Day -7, all patients are required to undergo treatment with medium-potency TCS using a standardized regimen according to the following guidelines:

- Apply medium-potency TCS, 1 fingertip unit for each 2% BSA, once daily to areas with active lesions. Low-potency TCS or TCI may be used on areas that cannot be treated safely with medium-potency TCS (eg, face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.)
- When lesions are under control, apply topical medication twice weekly; resume daily applications when lesions reactivate

- Monitor the patient for signs of local or systemic TCS toxicity and stop/adjust treatment as necessary

Typical TCS products to be used as standardized background treatment include triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment for medium-potency, and hydrocortisone 1% cream for low-potency. If patients have tolerance issues with any of these products or if they are not commercially available in some countries, they may substitute with products of the same potency from the list provided in the Study Reference Manual. On areas treated with TCS, moisturizers should be applied once daily only at the time when TCS is not applied (ie, do not use moisturizers and TCS on the same areas at the same time of the day). For

example, if TCS are applied in the evening, moisturizers will not be used in the evening on areas treated with TCS; however, will be applied to those areas in the morning. On areas not treated with TCS, moisturizers will be applied twice daily – morning and evening. The type, amount, and frequency of topical products used during the study will be recorded at home by patients in a medication log if possible, including the amount (number of fingertip units) used.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Storage and handling

1. Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.
2. Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound must be managed according to the rules provided by the Sponsor in the Pharmacy Manual.
3. The expiry date is mentioned on the IMP labels (when required by country regulation), and storage conditions are written on the IMP labels.
4. 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.
5. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. 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.
6. 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).
7. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

Preparation of IMP

Dupilumab or matching placebo in glass pre-filled syringes will be dispensed to the patients.

Responsibilities

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

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

maintained. For doses not given at study site, the home dosing diary will be used to record injections.

Any quality issue noticed with the receipt or use of an IMP/NIMP/device (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 8.3.7).

A potential defect in the quality of IMP/NIMP/device 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/NIMP/device and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP/device 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/NIMP/device to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP/device in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

A randomized treatment kit number list will be generated centrally by Sanofi for the IMPs. The IMPs (dupilumab or matching placebo) will be packaged in accordance with the list. The Sanofi Clinical Supply Chain team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system (Interactive Voice Response System/Interactive Web Response System [IVRS/IWRS]). This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the IMP to the patients. The Investigator obtains treatment kit number at randomization and subsequent scheduled visits via an IVRS/IWRS that will be available 24 hours a day.

At some site visits, the interactive response technology (IRT) will allocate enough kits for site administration on same day and home administration that will be performed 2 weeks later.

Randomization will be stratified: PSG (regardless of geographic location), US (non-PSG), Europe (non-PSG) and ROW (non-PSG).

A participant who has been allocated to a randomized intervention regardless whether the intervention kit was used or not (ie, participant registered by the IRT) will be considered a randomized subject. A participant cannot be randomized more than once in the study.

Dupilumab and placebo will be provided in identically matched 2 mL pre-filled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab / placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number

Patients will receive either;

- Dupilumab 600 mg (2 x 300 mg dupilumab injections) on Day 1 (ie, the loading dose), followed by 1 dupilumab injection of 300 mg Q2W until week 10, then 1 dupilumab +1 placebo injection at week 12 (to protect the blind while placebo patients receive their loading dose), followed by 1 dupilumab injection Q2W with last injection at week 22 or,
- Matching placebo for dupilumab (2 x 2 mL placebo injections) on Day 1 (ie, the loading dose), then 1 placebo injection Q2W until week 10, and then 2 x 300 mg dupilumab injections at week 12 (ie, the loading dose), followed by dupilumab injections Q2W with last injection at week 22.

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the patient.

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

Patient withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the patient will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the patient will not be withdrawn from treatment.

6.4 STUDY INTERVENTION COMPLIANCE

- Methods used by the Investigator or his/her delegate to ensure that the IMP was administered
- IMP accountability:
  - The Investigator or pharmacist will keep accurate records of the quantities of the IMP received, dispensed, used, unused, and returned/destroyed. The product accountability and inventory form/system is to be updated each time IMP is dispensed. It must be established with the Investigator or other personnel designated by the Investigator, and countersigned by the Investigator and the monitoring team. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to verify accountability and inventory.
  - Treatment kit number has to be recorded on the appropriate page of the electronic case report form (eCRF) and also on the product accountability and inventory form/system.
  - The monitor in charge of the study then checks the CRF data by comparing them with the IMP which he/she has retrieved and intervention log forms
  - All used, partially used, or unused treatments will be destroyed at each respective site, after accountability and reconciliation have been performed. The site must not destroy the unused IMP unless the Sponsor provides written authorization. Confirmation of destruction will be provided to the Sponsor.

- For more details regarding accountability, please refer to Pharmacy Manual.
- Intervention units returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

6.5.1 Prohibited Medications and procedures

Treatment with following concomitant medications is prohibited until the end of the study:

- Sedative anxiolytic or hypnotic treatments other than melatonin
- Patients taking systemic sedative antihistamines more than 5 days per week
- Lipophilic beta blockers, opioids, theophylline, clonidine, antidepressants or other medications known to interfere with sleep and AD as determined by the Investigators
- Live (attenuated) vaccine
- Immunomodulating biologics
- Investigational drugs
- High-potency and super-potent TCS, except when used for rescue
- Systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, CsA, AZA, MTX, MMF, JAK inhibitors, etc.), except when used for rescue

Study drug will be immediately discontinued if any of the following are used through week 24:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with an investigational drug
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, CsA, AZA, MTX, MMF, JAK inhibitors, etc.)

Note: If a patient receives rescue treatment with systemic corticosteroids or other systemic immunosuppressive drugs (CsA, AZA, MTX, MMF, JAK inhibitors, etc.), study treatment may be resumed if deemed appropriate by the Investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

The following procedures are prohibited during study participation:

- Phototherapy
- Tanning in a bed/booth

6.5.2 Permitted medications

The treatment with certain concomitant medications is permitted during the study. This includes:

- basic skin care (cleansing and bathing, including bleach baths),

- emollients (required as background treatment),

- topical anesthetics,

- topical antihistamines,

- systemic non-sedative antihistamines,

- systemic sedative antihistamines if taken ≤5 days per week on stable regimen for at least 1 month before randomization and stable regimens maintained throughout the study,

- and topical and systemic anti-infective medications for any duration.

If not specifically prohibited in Section 6.5.1 above, medications used to treat chronic diseases such as diabetes, hypertension, and asthma are also permitted; if there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor. The type, (active ingredient, formulation, strength, amount, frequency) of topical products used during the study will be recorded (eg, CRF, the source document). The amount of TCS used will be determined by evaluating the tube at each visit (see Study Reference Manual for details).

6.5.3 Rescue medicine

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. If possible, Investigators should attempt to limit the first step of rescue therapy to high-potency TCS and/or TCIs, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this, if necessary.

Note that:

1. Those who receive high-potency or superpotent TCS will be allowed to continue study treatment.
2. Those who receive systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, CSA, AZA, MTX, MMF, or JAK inhibitors) will discontinue study treatment for the duration of rescue + 5 half-lives of the rescue agent.

3. All patients will be encouraged to complete the entire schedule of study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD.

6.6 DOSE MODIFICATION

Dose modification of IMP for an individual patient is not allowed.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Intervention after the end of the study treatment is at the discretion of the Investigator or other treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The IMP should be continued whenever possible.

In case the IMP is stopped, it should be determined whether the stop can be made temporarily; definitive IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the CRF/eCRF. In any case, the participant should remain in the study for as long as possible through week 24.

Definitive intervention discontinuation is any intervention discontinuation associated with the definitive (permanent) decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP whatever the reason.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

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 CRF or eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Study drug dosing may be temporarily suspended in the event of:

- Intercurrent illnesses or major surgery
- Treatment with any prohibited concomitant medication or procedure (Section 6.5)

The Investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study intervention after temporary discontinuation should always be discussed with the medical monitor.

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.
- 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.
- See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. 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.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the CRF or 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. The site should document any case of withdrawal of consent.

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

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). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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.
- Patient-Reported Outcome (PRO) questionnaires and NRS should be completed by the patients before the consultation and/or clinical tests, 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.

8.1 EFFICACY ASSESSMENTS

8.1.1 Physician and Center Assessed Scales

8.1.1.1 Investigator's Global Assessment (IGA) (for eligibility during screening and baseline visits only)

Based on a 5-point scale ranging from 0 (clear) to 4 (severe), the IGA score is assessed at screening and baseline visits only, used as one of the inclusion criteria for determining patient's eligibility. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.1.2 Body Surface Area (BSA) Involvement of Atopic Dermatitis (for eligibility during screening and baseline visits only)

The BSA affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck (9%), anterior trunk (18%), back (18%), upper limbs (18%), lower limbs (36%) and genitals (1%) and will be reported as percentage of all major body sections combined. BSA is assessed at screening and baseline visits only, used as 1 of the inclusion criteria for determining patient's eligibility. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.1.3 Eczema Area Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (18). 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 will be collected at time points according to Section 1.3. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.1.4 SCORing of Atopic Dermatitis (SCORAD)

The 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 (European Task Force on Atopic Dermatitis 1993). There are 3 components to the assessment: A = extent or affected BSA, B = severity, and C = subjective symptoms. 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 (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) 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 analog 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 where the maximum is 103. Patients will undergo this assessment at time points according to Section 1.3. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.1.5 Polysomnography (PSG) (sub-study; conducted by the trained professional)

Polysomnography is a multi-parametric test used in the study of sleep (eg, biophysiological changes that occur during sleep) and as a diagnostic tool in sleep medicine. Polysomnography is typically performed at night and monitors many body functions. In this study, PSG is used to record sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), longest sleep episode, stages of sleep, sleep efficiency and arousal index.

For this PSG sub-study: 30 patients total (approximately 20 dupilumab and 10 placebo patients) will participate in the PSG sub-study. Each patient who participates in this sub-study will have a total of 3 overnight PSGs: at baseline timepoint, 2 (preferably) consecutive overnight PSGs to control for "first night effect" and collect baseline data; then 1 overnight PSG at week12. The procedure is detailed in Section 10.10 (Appendix 10).

8.1.1.6 Photography of Skin (not mandatory, site professional will be taking the photographs with patient's consent)

Photographs will be taken of representative areas of AD involvement using standard photography methodology at baseline. Photographs of the same area will be taken at subsequent clinic visits. Participating patients will be asked to sign a separate photography informed consent at Day 1/baseline.

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

8.1.2 Patient-Reported Outcome Scales (completed by patients)

Patients will be instructed on how to use the diary to record the required assessments at the screening visit. Clinical sites will receive alerts when patients do not complete diary items. Sites will be expected to contact patients who have missed 2 consecutive diary entries to encourage patient compliance.

8.1.2.1 Sleep Quality Numerical Rating Scale (NRS)

- Sleep Quality NRS (0-10), collected daily including 7 days immediately preceding the baseline visit (or daily for 5 days (from Day -7 to Day -3 prior to baseline) for patients participating in the PSG sub-study), and daily for 4 weeks (through visit 4), then daily during the week before each planned visit.
- Sleep Quality NRS to collect information on patient-reported quality of sleep. Numerical rating scale range is from 0 ("worst possible sleep") to 10 ("best possible sleep"). The assessment tool is provided in Section 10.9 (Appendix 9).

  Note: The analytic plan to define a clinically relevant, within-person response threshold on the sleep NRS will be described in a separate validation plan.

8.1.2.2 Sleep Diary

Collected daily including 7 days immediately preceding the baseline visit, and daily for 4 weeks (through visit 4), then daily during the week before each planned visit.

A sleep diary is designed to gather information about patient's daily sleep pattern. Sleep diary will measure night-time sleep assessments.

If possible, it should be completed within 1 hour of getting out of bed in the morning. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.3 Peak pruritus Numerical 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 the following questions:

"On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"

Patients will complete the rating scale daily for 7 days prior to baseline (or daily for 5 days (from Day -7 to Day -3 prior to baseline) for patients participating in the PSG sub-study), and daily for 4 weeks (through visit 4), and then daily during the week before each planned visit. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.4 Skin pain Numerical Rating Scale (NRS)

Patients will be asked to rate their skin pain using a 0 to 10 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?"

Patients will be asked to complete this assessment scale daily from 7 days prior to baseline through week 4 (visit 4), and then daily during the week before each planned visit. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.5 Skin sensitivity to touch Numerical Rating Scale (NRS)

Patients will answer the question: "Think about all the areas of your skin with eczema. How sensitive was your skin at its worst in the past 24 hours?"

Patients will be asked to complete this assessment scale daily from 7 days prior to baseline through week 4 (visit 4), and then daily during the week before each planned visit. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.6 Skin burn Numerical Rating Scale (NRS)

Patients will answer the 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?"

Patients will be asked to complete this assessment scale daily from 7 days prior to baseline through week 4 (visit 4), and then daily during the week before each planned visit. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.7 PROMIS Sleep Related Impairment Short Form 8a

The patient-reported outcomes measurement information system (PROMIS) is a DSM-5, Level 2, sleep disturbance measure. This study uses the 8-item PROMIS Sleep Related Impairment Short Form that assesses the domain of sleep related impairment in the past 7 days in individuals age 18 and older.

Each item asks the patient to rate the severity of the patient's sleep related impairment during the past 7 days. Each item on the measure is rated on a 5-point scale (1 = not at all; 2 = a little bit; 3 = somewhat; 4 = quite a bit; and 5 = very much) with a range in score from 8 to 40 with higher scores indicating greater severity of sleep impairment. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.8 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life (ASP), or their 'daytime sleepiness'.

8.1.2.9 Patient oriented eczema measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess frequency of disease symptoms in children and adults (9). 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. The questionnaire will be administered at time points according to SoA (Section 1.3). The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.10 Dermatology life quality index (DLQI)

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QoL (10). The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QoL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QoL. The questionnaire will be administered at time points according to SoA (Section 1.3). The assessment tool is provided in Section 10.9 (Appendix 9)

8.1.2.11 Hospital anxiety and depression scale (HADS)

The hospital anxiety and depression scale (HADS is an instrument for assessing symptoms of anxiety and depression in non-psychiatric populations; repeated administration also provides

information about changes to a patient's emotional state (11, 12). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The questionnaire will be administered at time points according to Section 1.3. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.12 Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis

The Work Productivity and Activity Impairment Questionnaire for AD (WPAI-AD) is designed to assess the impact of AD on the patient's productivity. The WPAI is a 6-item, validated questionnaire to measure impairments in work and activities over a 7-day recall period. The WPAI-AD outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. The questionnaire will be administered at time points according to SoA (Section 1.3). The WPAI-AD is provided in Section 10.9 (Appendix 9).

8.1.2.13 Days missed from school or from work due to AD

Patients will complete questions about their current employment status and days missed from work/school due to their AD for all patients who are working/going to school (internally developed). This questionnaire is provided in Section 10.9 (Appendix 9).

8.1.2.14 ACQ-5 (among those reporting asthma at baseline)

The 5-question version of the Juniper asthma control questionnaire (ACQ) is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of patients with a medical history of asthma, at time points according to SoA (Section 1.3). The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.2.15 Allergic Rhinitis-visual analog (AR-VAS) (among those reporting allergic rhinitis at baseline)

The allergic rhinitis-visual analog scale (AR-VAS) is a validated instrument for the documentation of symptoms and therapy monitoring in allergic rhinitis. Patients with comorbid AR will be provided with an ungraded VAS and will be asked to place a mark on the scale to indicate the severity of AR symptoms. Patients will be asked: "Overall how much are your allergic symptoms bothering you today?" The VAS extremities will be noted as "Not at all bothersome" to the left and "Extremely bothersome" to the right. This questionnaire will be administered at baseline and then quarterly (±2 weeks) throughout the study to the patients with AR at baseline and to patients who develop AR during the study. The assessment tool is provided in Section 10.9 (Appendix 9).

8.1.3 Performance-Reported Outcome scales

8.1.3.1 Actigraph (patients will be trained how to wear the actigraph 7 days before baseline):

Wrist actigraphy is a technique for measuring movement of a limb over an extended recording period (days to weeks). The signals generated by wrist movement are sensed by a tiny microcomputer contained within the watch and translated into activity counts.

Actigraphy is being worn on the wrist of the non-dominant hand in this study to provide estimates of the duration, timing and patterns of sleep in study participants (eg, TST, SOL, WASO, and sleep efficiency). Eligible patients will wear an Actiwatch during the 7 days immediately preceding the baseline visit, daily through week 4 (visit 4), and then daily during the week before each planned visit. A detailed description of the device is provided in Section 10.8 (Appendix 8). An operational manual will be provided to Investigators.

8.1.3.2 Psychomotor vigilance test (patients will be instructed by the site professional and will administer the tests themselves)

The psychomotor vigilance test (PVT) is a widely used measure of behavioral alertness, having a high sensitivity to sleep deprivation (13). There are several versions of the PVT, but the standard form lasts 10 minutes and assesses sustained attention/vigilance by recording response times to stimuli that occur at varying inter-stimulus intervals. The PVT assesses vigilance by sampling many responses to stimuli appearing at random inter-stimulus intervals (eg, between 2 seconds and 10 seconds) occurring over a period of time (ie, 10 minutes). The patient is instructed to monitor an area on a computer/iPad/electronic screen and then to press a response button as soon as the stimulus appears in order to keep the response time as low as possible without pressing the button prematurely.

8.1.3.3 Neurocognitive test (patients will be instructed by the site professional and will administer the tests themselves)

The automated neuropsychological assessment metrics (ANAM computerized cognitive testing battery includes tests suitable for studies of human performance as well as for studies in the areas of both operational and traditional clinical medicine. The tests are administered by a computer/iPad/electronic device and subjects need only to use the 2 mouse buttons to respond. For each of the tests, patients will be provided instructions that describe how to take the test and indicate a correct response. Research has shown that ANAM's sensitivity enables it to detect the subtle cognitive deficits often observed in various medical conditions (14). Further, clinical trial data indicating that ANAM can detect subtle medication-related cognitive changes, suggest that it is ideal for use in the current investigation (15). The following is a list of individual ANAM measures and a description of each test to be used in this study.

- Running Memory assesses sustained attention, working memory, and resistance to interference. The test requires sustained attention in response to a stimulus on the computer screen during a forced-pace, rapid task. Numbers are presented on the screen

and the user must press a specified key indicating whether the number is the same as or different than the previous number. The subtest takes approximately 5 minutes to complete.

- Mathematical Processing assesses mathematical computation and working memory. The test involves Math problems being presented on the screen. The answer must be figured out and then the user must decide if the answer is > or < the number 4. The subtest takes approximately 5 minutes to complete.
- Procedural Reaction Time is an assessment of choice reaction time. The user must tap the left mouse button if the number shown on the screen is 2 or 3 and the right mouse button if the number shown on the screen is 4 or 5. The subtest takes approximately 3 minutes to complete.

8.1.4 Multiplicity considerations

Multiplicity is considered for testing multiple endpoints. In order for any secondary endpoints to be eligible for being declared significant, the primary endpoint must be significant.

For the secondary endpoints, the overall type I error rate will be controlled at the 2-sided 0.05 level using a sequential testing procedure. The order in which the secondary endpoints are tested will be specified in the Statistical Analysis Plan.

Each endpoint will be tested at 0.05 (2-sided) level of significance. If at any step the null hypothesis of superiority is rejected, the endpoints listed below that will not be technically eligible for being declared significant. Regardless of eligibility, all endpoints will be tested.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Vital signs

Vital signs, including heart rate, sitting blood pressure, body temperature, and respiration rate, will be collected pre-dose at time points according to Section 1.3. All vital signs will be taken at screening visit and all subsequent visits before injection and at 30 minutes (± 10 minutes) post-injection (during the in-clinic 30-minutes post-injection observation). In case a patient comes to the study site for IMP injection by the study staff at weeks 6, 10, 14, 18, and/or 22, vital signs will also be measured at these visits, as for other planned on-site visits.

8.2.2 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the SoA (Section 1.3).

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered

clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, 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 or severe hypersensitivity reactions
- Malignancy (except in situ carcinoma of the cervix, non-metastatic squamous or basal cell carcinoma of the skin)
- Helminthic infections
- Suicide-related events
- Any type of conjunctivitis or blepharitis (severe or serious)
- Keratitis

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

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP:
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Section 10.3 [Appendix 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 should be conducted until the outcome has been determined (See Section 10.4 [Appendix 4]).
- Symptomatic overdose (serious or nonserious) with IMP/noninvestigational medicinal product (NIMP):
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least

twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

- Injectable administration: at least twice the dose during the planned intervals

- The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

AE 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 procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs, serious or nonserious, will be collected from the signing of the ICF until the end of study at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3 (Appendix 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, 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 should promptly notify the Sponsor.

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

8.3.2 Method of detecting AEs and SAEs

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.

8.3.3 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 nonserious AEs of special interest (as defined in Section 8.3), 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 given in Section 10.3 (Appendix 3).

8.3.4 Physical examinations

- A thorough and complete physical examination will be performed at time points according to Section 1.3.
- Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.
- 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 adverse event.

8.3.5 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, IRB/ IEC, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing a SAE or 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.

8.3.6 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until outcome is known.

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 Section 10.4 (Appendix 4).

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP/NIMP/device 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.

8.4 TREATMENT OF OVERDOSE

Symptomatic overdose of IMP is an AESI (defined in Section 8.3). No specific treatment is available for IMP overdose.

In the event of a symptomatic overdose, the Investigator/treating physician should:

1. Contact the medical monitor immediately
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study interventions can no longer be detected systematically
3. Obtain a plasma sample for PK analysis within as soon as possible, from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis)
4. Document the quantity of excess dose as well as the duration of the overdose in the CRF.

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

8.5 PHARMACOKINETICS

PK parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS

Not applicable.

8.8 BIOMARKERS

Not applicable.

8.9 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Work productivity and Activity Impairment Questionnaire AD and Days missed from school or from work due to AD are included for assessing this category.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The alternative statistical hypothesis tested is that the effect of dupilumab on sleep quality and quantitative components (eg, sleep efficiency, TST, etc.) as well as on general AD related efficacy assessments in adult patients with moderate to severe AD and sleep disturbance is superior to placebo.

9.2 SAMPLE SIZE DETERMINATION

The sample size calculations were based on the subset of patients who reported ≥5 units of baseline sleep loss and ≥3 units of baseline pruritus scores on the SCORAD instrument in a previous study (AD1424) evaluating efficacy of dupilumab for AD.

Since no previous data are available on daily sleep on the NRS scale, the SCORAD sleep component (VAS) data was used as a basis for the sample size determination for the primary endpoint. The variability (standard deviation) estimate for the subset of patients mentioned above was 37% for the % change from baseline to week 12. Given the uncertainty in the variability from this variable to the NRS weekly average sleep score, the above variability was inflated by ~20%, and assumed to be 44% for the primary sleep parameter. With these assumptions, a total sample of 150 (50 in placebo and 100 in dupilumab group) patients will provide 90% power (alpha = 0.05, 2-sided) to detect a treatment difference of 25% (effect size, $\Delta/\sigma = 0.57$) for the percent change from baseline.

For secondary actigraphy endpoints, sample size estimates are provided in reference to nemolizumab Ph2 data at week 4. For TST, to detect a 30 minutes difference between treatments: (2:1 allocation ratio; alpha=0.05, 2-sided), assuming the same variability at week 16 weeks as seen for nemolizumab at week 4 (=56 min), then 167 subjects are needed to provide 90% power. Furthermore, the proposed sample size would have >90% power to detect a difference of 10% for change from baseline in actigraph based sleep efficiency, assuming a variability of 11% (alpha=0.05, 2-sided). The variability estimate was based on (8) for actigraphy based sleep efficiency at week 4, inflated by 50% to account for possible increase in variability over time (from week 4 to week 16). Of note, the data used for actigraphy parameters are limited.

Allowing for drop outs, a total of approximately 201 patients will be enrolled in the study.

Considering the uncertainty of the variability of the primary endpoint, when data are available for this endpoint from about 50% of the patients, the variability will be assessed in a blinded manner, and the sample size will be re-estimated. If the re-estimated sample size is higher than the original estimate, the sample size may be increased accordingly, not to exceed a total of 150 additional patients.

Since this analysis will be performed in a blinded manner, no adjustment to the type I error will be made in the final analysis.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 3.

Table 3 - Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	The randomized population includes all patients with a treatment kit number allocated and recorded in the IRT database, and regardless of whether the treatment kit was used or not. Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population, but will be included in the safety population.
Intent-to-treat (ITT)	All randomized patients, and will be analyzed according to the treatment group allocated by randomization
Efficacy	The ITT Population
Safety	The safety population includes all patients who actually received at least 1 dose or partial dose of the IMP, analyzed according to the treatment actually received. Randomized patients for whom it is unclear whether the study medication was taken will be included in the safety population as randomized.

Abbreviations: ICF = informed consent form; IRT = interactive response technology; ITT = intent-to-treat

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

Note: All daily assessments (eg, sleep NRS, actigraphy parameters, sleep diary, etc.) will be analyzed as weekly averages for the week immediately preceding the study visit. Thus, the baseline value will correspond to the assessments completed during the week preceding randomization.

Table 4 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary Percent change from baseline to week 12 in sleep NRS	Percent change from baseline will be analyzed using a mixed effect model with repeated measures (MMRM) with treatment, baseline value, randomization stratum, week, treatment by week interaction, and baseline value by week interaction terms (all as fixed effects) in the model. An unstructured correlation matrix will be used to model the within-patient errors. No imputations for missing values will be carried out for the primary analysis. LS mean changes between the dupilumab group and placebo, the corresponding 95% CI of the differences and p-values will be provided.

Secondary	
Change from baseline to week 12 in sleep efficiency, total sleep time, wake after sleep onset, sleep onset latency based on actigraph data	The similar approach as for the analysis of primary endpoint will be used.
Percent change from baseline to week 12 in Pruritus NRS	A similar approach as for the analysis of primary endpoint will be used.
Change from baseline to week 12 in SCORing Atopic Dermatitis (SCORAD) total score	A similar approach as for the analysis of primary endpoint will be used.
Change from baseline to week 12 in SCORAD sleep VAS	A similar approach as for the analysis of primary endpoint will be used.
Change from baseline to week 12 in Dermatology Quality Life Index (DLQI)	A similar approach as for the analysis of primary endpoint will be used.
Change from baseline to week 12 in Patient Oriented Eczema Measure (POEM) total score	A similar approach as for the analysis of primary endpoint will be used.
Change from baseline to week 12 in PROMIS Sleep Related Impairment SF8a total score Proportion of patients with EASI50, EASI75 (reduction of EASI score by ≥50% and ≥75% from baseline, respectively) at each time point	will be analyzed via the Cochran-mantel-Haenszel test adjusted by the randomization stratum at each time point
Exploratory	Will be described in the statistical analysis plan finalized before database lock prior to the week 12 interim analysis. Of note, formal statistical comparisons will not be performed on the PSG endpoints due to the limited sample size of the sub-study; the analyses will be limited to providing summary statistics for the specified endpoints.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Population.

Table 5 - Safety analyses

Endpoint	Statistical Analysis Methods
AE, SAE, AE leading to death, AE leading to permanent treatment discontinuation	Treatment emergent adverse event (TEAE) incidence tables will be presented by system organ class (SOC), high-level group term (HLGT), high-level term (HLT) and preferred term (PT) for each treatment group and overall, showing the number (n) and percentage (%) of patients experiencing a TEAE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study drug. AEs that occur outside the treatment emergent period will be summarized separately. Proportion of patients with at least 1 TEAE, treatment emergent SAE, TEAE leading to death, and TEAE leading to permanent treatment discontinuation will be tabulated by treatment group and overall. All Tables will be provided separately for the double-blind treatment period, and for the entire study.

9.4.3 Other analyses

Not applicable.

9.5 INTERIM ANALYSES

After all patients have completed the 12 weeks of double-blind, randomized treatment period, the database for this portion of the study will be locked, and the study will be unblinded; Comparative efficacy data will be analyzed following this database lock.

Since the unblinding will be performed after the randomized treatment period, no adjustments to the type I error is needed.

Once all patients complete the 24 weeks post randomization, the final database lock will be performed, and the remaining data will be analyzed.

9.6 DATA MONITORING COMMITTEE (DMC)

No DMC 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 Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, 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.
  - 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.

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 (if acceptable by local regulations) 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 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.

Participants who are rescreened are required to sign a new ICF.

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 signature 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 signature.

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 Global Data Protection Regulation.

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.

Subject race and ethnicity will be collected in this study because these data are required by several regulatory agencies (eg, on afro American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- 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.

- 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.
- 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.

10.1.5 Committees Structure

Not applicable.

10.1.6 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publicly 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.

10.1.7 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.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- 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 end of the clinical study 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.

10.1.8 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.
- Definition of what constitutes source data can be found in Study Reference Manual.

10.1.9 Study and Site Closure

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 the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- 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 recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

10.1.10 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

- Urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) will be performed by the local laboratory.
- The local laboratory results used to make a study intervention decision or response evaluation must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

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, electrocardiogram [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).
- 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.

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

a) 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.

b) 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.

c) 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.

d) Is a congenital anomaly/birth defect

e) 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 1of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 to Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. 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 to Sponsor.
- 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 to Sponsor. 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 to** Sponsor.
- 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 1of 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 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 Sponsor with 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.

REPORTING OF SAES

SAE reporting to Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- 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 [medical monitor/SAE coordinator] by telephone.
- Contacts for SAE reporting can be found in Study Reference Manual.

SAE reporting to Sponsor via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to report the SAEs when the electronic system is unavailable for more than 24 hours or when the electronic system has been taken off-line. The guidelines for reporting SAEs via paper CRF will be provided in the Study Reference Manual.
- 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.
- Contacts for SAE reporting can be found in Study Reference Manual.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

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

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

   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, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1of 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 enrollment.

CONTRACEPTION GUIDANCE

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 6.

In addition, WOCBP must refrain from donating ova for the duration of the study and for 12 weeks after the last dose of study intervention.

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[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*

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 intervention. 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.

b Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the intervention period and for at least [X, corresponding to time needed to eliminate study intervention plus 30 days for study interventions with genotoxic potential] after the last dose of study intervention.

PREGNANCY TESTING:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Standard urine pregnancy testing will be performed for WOCBP participants throughout the study (see study SOA Section 1.3).
- Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

COLLECTION OF PREGNANCY INFORMATION:

Male 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 study intervention.
- 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 participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. 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 will be reported as an AE or SAE. A spontaneous abortion 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 8.3.5. 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 and be withdrawn from the study.

10.5 APPENDIX 5: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."
Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

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

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.6 APPENDIX 6: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.7 APPENDIX 7: ABBREVIATIONS

AASM:	American Academy of Sleep Medicine
ACQ:	asthma control questionnaire
AD:	atopic dermatitis
ADRs:	adverse drug reactions
AE:	adverse events
AESI:	adverse event of special interest

ANAM:	automated neuropsychological assessment metrics
AR-VAS:	allergic rhinitis-visual analog scale
AZA:	azathioprine
BSA:	body surface area
CIOMS:	Council for International Organizations of Medical Sciences
CRFs:	case report forms
CsA:	systemic cyclosporine A
DTP:	Direct To Patient
EASI:	eczema area severity index
ECG:	electrocardiogram
eCRF:	electronic case report form
FSH:	follicle stimulating hormone
GSO:	Global safety officer
HADS:	hospital anxiety and depression scale
HbA1c:	hemoglobin A1c
IB:	Investigator's Brochure
ICF:	informed consent form
IEC:	Independent Ethics Commitees
Ig-4:	immunoglubulin-G4
IGA:	Investigator's global assessment
IL 4Rα:	IL-4 receptor alpha
IL 4Rα/γc:	IL-4 signaling via the Type I receptor
IL-13:	interleukin-13
IL-4:	interleukin-4
IL-4Rα/IL-13Rα:	IL-4 and IL-13 signaling through the Type II receptor
IMP:	investigational medicinal product
IRB:	Institutional Review Boards
IRT:	Interactive response technology
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
JAK:	Janus Kinase
MMF:	mycophenolate mofetil
MMRM:	mixed model effect model
MTX:	methotrexate
NIMP:	noninvestigational medicinal product
PI:	Prescribing Information
PSG:	polysomnography
PVT:	psychomotor vigilance test
Q2W:	every 2 weeks
QoL:	quality of life
QW:	every week
SC:	subcutaneously
SCORAD:	SCORing atopic dermatitis
SoA:	Schedule of Activities
SOL:	sleep onset latency

TCI:	Topical Calcineurin Inhibitor
TCS:	topical corticosteroids
Th2:	T-helper Type-2
TST:	total sleep time
VAS:	visual analog scale
WASO:	wake after sleep onset
WPAI-AD:	work productivity and activity impairment questionnaire for atopic dermatitis

10.8 APPENDIX 8 ACTIGRAPHY

Actigraphy is an objective and convenient method for assessing quantitative sleep parameters in multiple sleep related conditions. In this study a most advanced and acceptable by the regulatory authorities device will be selected. A thorough review of the existing literature revealed reliable and validated devices such as Actiwatch Spectrum (Philips/Respironics, Murrysville, PA).

Wrist actigraphy is a technique for measuring movement of a limb over an extended recording period (days to weeks). The signals generated by wrist movement are sensed by a tiny microcomputer contained within the watch and translated into activity counts. Algorithms have been developed to translate these activity counts or "epochs" (or "periods") that correspond to times when a person is likely to be asleep or wake. Actigraphy provides the ability to estimate sleep duration, sleep patterns (including timing of sleep and napping) and disturbed sleep (awakenings during the sleep period) more accurately than questionnaire. It is easier to use than other approaches such as polysomnography.

Actigraphy is being performed in this study to provide reliable estimates of the duration, timing and patterns of sleep in study participants.

The equipment that will be used for this study, the Actiwatch Spectrum® (from Philips Respironics, Inc.) is a small device that will be worn on the non-dominant wrist. The Actiwatch Spectrum® contains a solid-state piezoelectric accelerometer (sensitive to 0.025G and above), lithium battery, microprocessor, nonvolatile 1 MB of memory, and associated circuitry. The orientation and sensitivity of the accelerometer are optimized for highly effective sleep/wake inference from wrist activity, which has been previously validated.

The device is designed to be compact, lightweight, waterproof, and to detect movement, time "off the wrist" and environmental light. After the watch data are scored by a selected expert center, a number of summary measurements will be generated for each participant, including: average sleep duration and sleep efficiency (percentage of time in bed spent asleep).

During the beginning of the study the patients will be shown how to use the sleep watch. The participant will be instructed to wear the watch on the non-dominant wrist for 7 days 24 hour periods (minimum of 5 nights, including at least 1weekend/non-work day period). The watch will be worn 7 evenings of sleep before each clinical visit. The participant also will be instructed on

completing a diary concurrently (see Section 10.9, Appendix 9). This will provide a "backup" in case there are questions about the recording.

Steps to process actigraphy data and send them to the Reading Center are described in detail in a Site Coordinator Manual.

An actigraph log should be maintained at the clinic so that the locations of the Actiwatch devices are known at all times. A serial number (EX. A01785) for each Actiwatch can be found on the backside of each Actiwatch. This should be used as the Actiwatch ID.

QUALITY ASSURANCE FOR THE ACTIWATCH

Each research personnel charged with the responsibility of initializing, downloading or any other handling of the Actiwatch will be required to meet performance standards that indicate an understanding of the Actiwatch's battery life, use of communications dock and software, and explaining the Actiwatch and sleep diary completion to the participant. Only personnel who meet these standards will be certified and approved to handle the Actiwatch devices and instruct the participants.

Personnel will be required to attend a training session, or undergo local training by a certified technician.

Training will consist of:

1. Overview of Actigraphy Operations Manual, including detailed use of Actiwatch, the software, and the communications dock
2. Hands on training for initializing and downloading/saving of files
3. Overview of Actiware Spectrum® Software Manual

CERTIFICATION

Each staff member handling the Actiwatch devices needs to successfully complete 3 initializations, downloading, file checking, and the saving to the assigned folder.

10.9 APPENDIX 9: CLINICIAN-REPORTED OUTCOMES (CLINROS) AND PATIENT-REPORTED OUTCOMES (PROS)

1. **IGA (completed by Investigator at screening and baseline visits only)**

IGA Scale

2. Body Surface Area of Atopic dermatitis Involvement (BSA) (completed by Investigator at screening and baseline visits only)

Derived from "Measurement of involved surface area in patients with psoriasis", by B. Ramsay and C.M. Lawrence. British Journal of Dermatology (1991) 124, 565-570. Copyright © 1991 The Newcastle upon Tyne Hospitals NHS Foundation Trust
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3. EASI (Reference for the Investigator)

EASI scale

How to Use EASI

The EASI scoring system uses a defined process to grade the severity of the signs of eczema and the extent affected:

1. Select a body region

Four body regions are considered separately:

- Head and neck
- Trunk (including the genital area)
- Upper extremities
- Lower Extremities (including the buttocks)

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a score of between 0 and 6 based on the percentage involvement. Precise measurements are not required.

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

To aid in your body region grading you can use the diagrams in Appendix 1.

3. Assess the severity of each of the four signs in that body region:

1. Erythema
2. Edema/papulation
3. Excoriation
4. Lichenification

Further explanations of these terms can be found in FAQ's (Appendix 4)

Grade the severity of each sign on a scale of 0 to 3:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved region.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)
- ✓ Palpation may be useful in assessing edema/papulation as well as lichenification

To aid your severity grading, a photographic atlas of suggested categories is available in Appendix 2

Remember: *Include only inflamed areas in your assessment; do not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or post inflammatory pigmentation changes.*

EASI guidance December 14

How to record your scores

The assessed parameters are inserted into a table (example shown below for age≥8 years). The final EASI score ranges from 0-72.

Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	x	x 0.1	
Trunk	(+	+	+	)	x	x 0.3	
Upper extremities	(+	+	+	)	x	x 0.2	
Lower extremities	(+	+	+	)	x	x 0.4	
The final EASI score is the sum of the 4 region scores							——— (0-72)

Two forms of the EASI scoring system are available depending on the age of the patients. The multipliers for the region score are different in the under 8's version to reflect the relative proportion of body regions in young children:

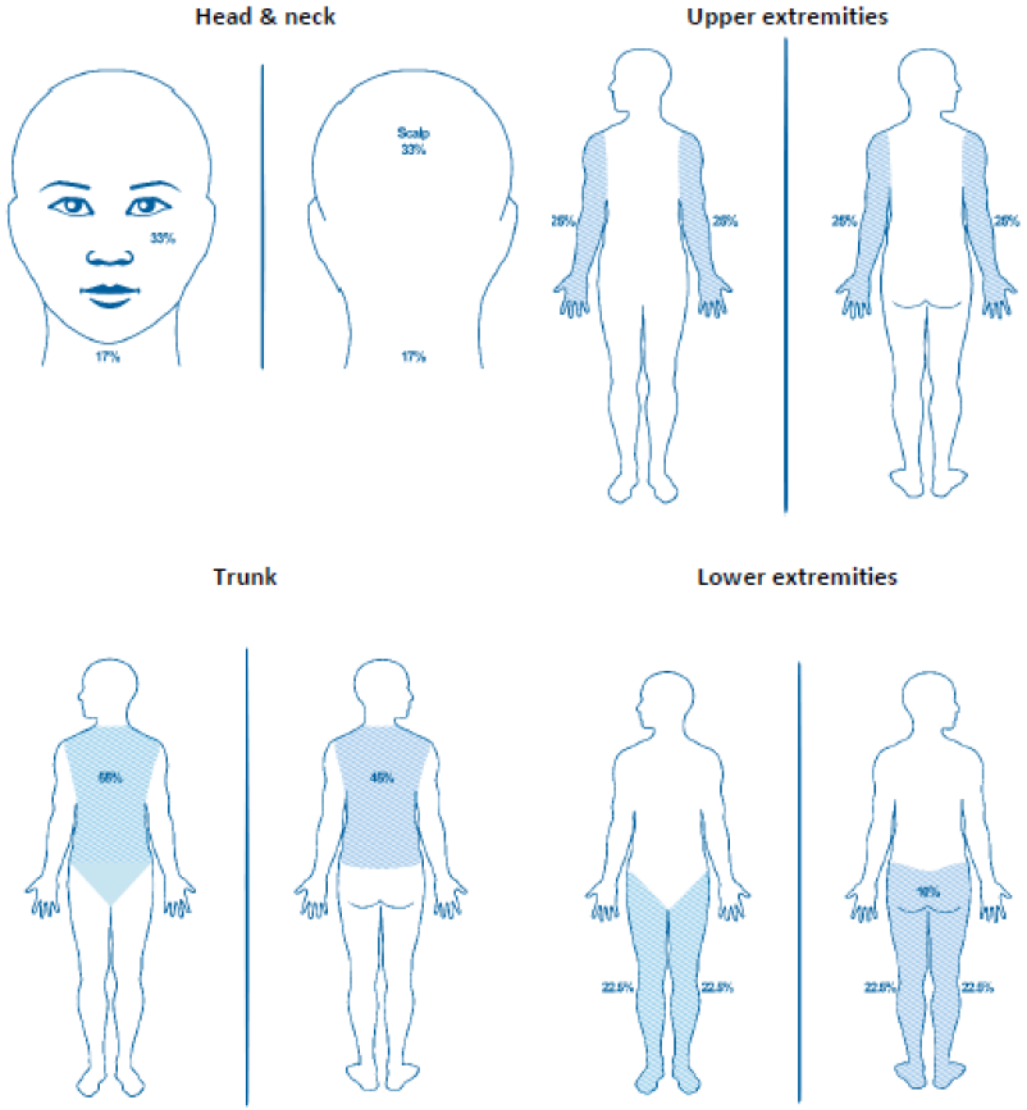
- Patients 8 years or above
- Patients under 8 years of age.

The forms can be found in appendix 3.1 and 3.2 and also as word documents on the HOME website (www.homeforeczema.org)

EASI guidance December 14

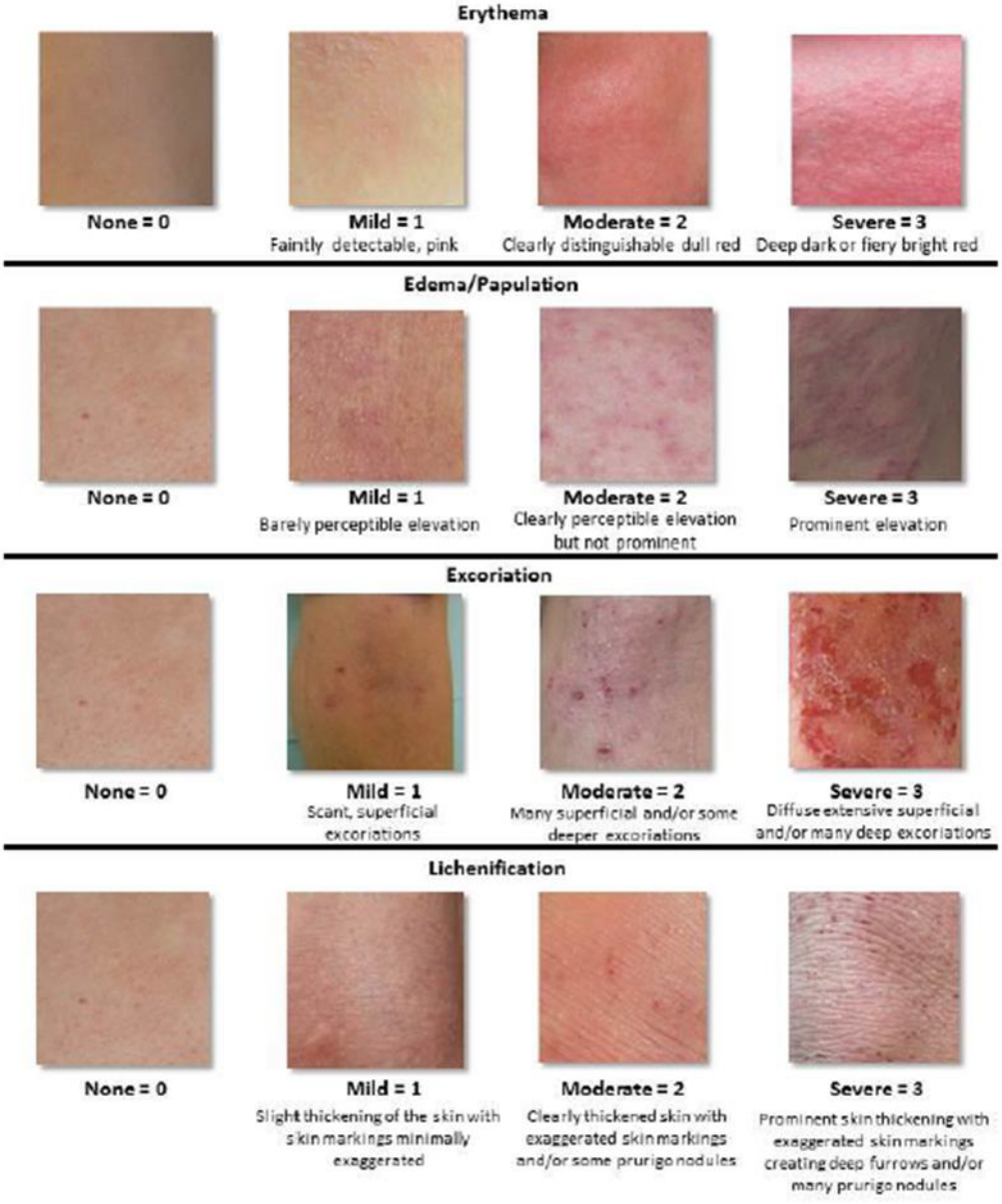
Appendix 1: Eczema Area and Severity Index (EASI) - Extent of eczema per body region

Score each region from 0 to 100%



EASI guidance December 14

Appendix 2: Eczema Area and Severity Index (EASI) –lesion severity atlas



EASI guidance December 14

Appendix 3.1: Eczema Area and Severity Index (EASI) case report form – age <8 years

Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	**None**
1	**Mild**
2	**Moderate**
3	**Severe**

- ✓ Take an average of the severity across the involved area.
- ✓ Half points may be used e.g. 2.5.

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	X	X 0.2	
Trunk	(+	+	+	)	X	X 0.3	
Upper extremities	(+	+	+	)	X	X 0.2	
Lower extremities	(+	+	+	)	X	X 0.3	
						The final EASI score is the sum of the 4 region scores:	_____ (0-72)

EASI guidance December 14

Appendix 3.2: Eczema Area and Severity Index (EASI) case report form - age≥8 years

Area of Involvement: Each body area has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points may be used e.g. 2.5.

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification(0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	x	X 0.1	
Trunk	(+	+	+	)	x	X 0.3	
Upper extremities	(+	+	+	)	x	X 0.2	
Lower extremities	(+	+	+	)	x	X 0.4	
The final EASI score is the sum of the 4 region scores:							_____ (0-72)

EASI guidance December 14

Appendix 4 - Frequently Asked Questions

What is the difference between edema/papulation and lichenification?
Consider edema/papulation as corresponding to the acute signs of atopic dermatitis that reflect histological spongiosis. Lichenification are more firm thickened plaques with accentuation of the skin markings that develop as a result of prolonged scratching or rubbing in chronic disease. In darker skin types, follicular lichenification may present as firm flat-topped discrete papules. Grade these chronic lesions as lichenification.

How do I grade prurigo nodules?
Prurigo nodules are larger, deeper lesions as a result of chronic scratching and are graded as areas of lichenification.

How do I grade erythema in darker skin?
To avoid underestimating inflammation in patients with darker skin tones, take into account the underlying skin pigment when grading erythema. Often this means increasing your erythema grade by one level.

Can half-steps be used to assess lesion severity?
The original EASI validation study allowed for half steps. These may be helpful when trying to average the severity of a parameter over a region. For example, if there are some areas with an erythema grading of 2 and some areas more consistent with a severity of 3, 2.5 may be a good choice.

What if most areas in a region are a severity grade of 1, but there are some areas that are a grade 3?
Attempt to average the severity across the involved areas in that region. If these areas are close to equal in size, a score of 2 would be most appropriate. If the majority of involved areas are a grade 1, a score of 1 or 1.5 is more appropriate. Be careful not to score the highest severity in a region but the average one.

How do I grade xerosis (dryness), ichthyosis and hyperlinear palms?
Unless there is active acute or chronic eczema overlying these findings, they are not included in the EASI assessment.

How precise should my assessment of eczema extent be?
The *region scores*, which reflect the extent of eczema, were designed and validated as rough estimates of the percentage of involved skin. Each region is given a *score* ranging from 0 to 6, based on a "ballpark" estimation of extent (see region score table in page 1). If you find it difficult to provide a rough estimate of disease extent, you can use the schematics in Appendix 1 to guide you. More time-consuming methods for evaluating disease extent such as the rule of nines or the 'palm' method are generally unnecessary, as the EASI was designed to be…easy.

EASI guidance December 14

My patient has responded well to treatment and significantly improved since the last visit. Should I adjust the grading based on the patient's relative improvement?
No. The EASI is a static score, meaning that it is done independently at each time point to reflect current severity. You should grade the EASI per visit regardless of the previous status. Studies have shown that the EASI score has good responsiveness, meaning that overall it is sensitive to change and the improvement will be reflected in the total score.

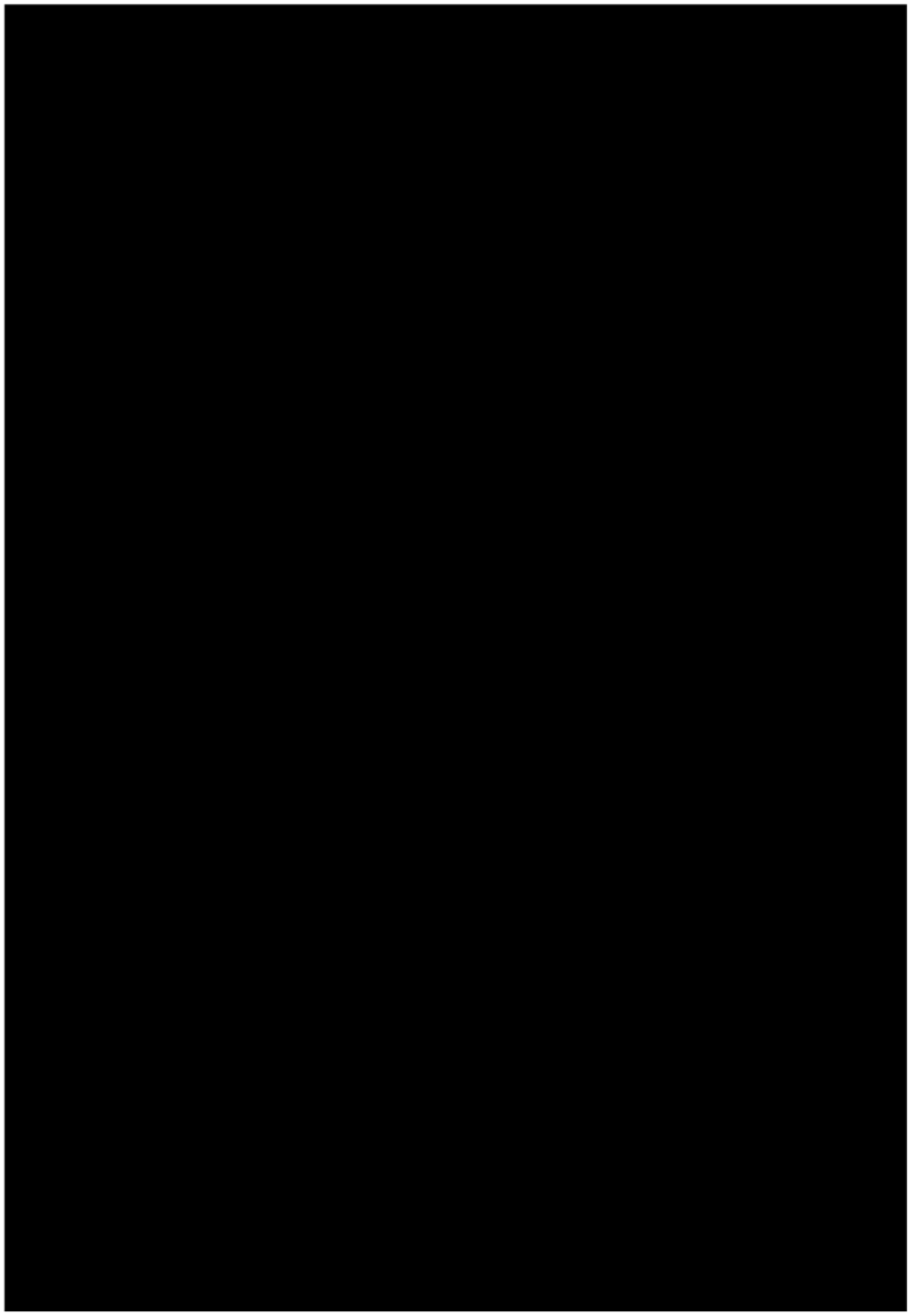
Can the EASI be used in children?
Yes. The EASI is performed in the same method in all age groups, but the calculation of the final EASI score differs by age. When calculating the EASI, each of the 4 region scores is multiplied by a constant which reflects the relative contribution of that region to the total body surface area. For patients 8 years and older the multipliers are 0.1 for the head/neck, 0.2 for the upper extremities, 0.3 for the trunk and 0.4 for the lower extremities. Below 8 years of age the head/neck multiplier is increased to 0.2 while the lower extremities multiplier decreases to 0.3, consistent with the proportions of these regions in childhood. Refer to Appendix 3 for EASI forms by age.

What happens if a child turns 8 during the course of the study? Which EASI formula should I use?
There are no clear-cut definitions for this situation. In general, if the study is a short term study such as an RCT lasting a few months – using the same formula throughout the trial is preferred, even if the child turns 8 during these months. Keeping the EASI formula consistent in this scenario can serve to preserve the EASI sensitivity to change (e.g. its change in response to treatment) without compromising the validity of the score.
In long term studies such as cohort studies lasting a year or longer, it is important to update the EASI formula based on the physical changes children go through. Switching to the age 8+ formula once a child is older is preferred in that scenario.

What do the terms erythema, edema/papulation, excoriation and lichenification mean?
These are key signs of atopic dermatitis. Recognizing and grading them properly requires training on the visual and physical exam consistent with these signs. Generally speaking, erythema is skin redness; edema/papulation refers to an elevation or swelling of the skin (that should be differed from lichenification below); excoriations are scratch marks that have broken the skin surface; and lichenification is a leathery thickening of the skin with exaggerated skin markings.

EASI guidance December 14

4. Scoring of Atopic Dermatitis (SCORAD) (completed by Investigator)



5. Sleep Quality NRS (completed by patients)

Instructions: Please complete the following question upon awakening for the day.

Select the number that best describe the quality of your sleep last night.

0	1	2	3	4	5	6	7	8	9	10
Worst possible sleep										Best possible sleep

6. Atopic dermatitis Sleep Diary (completed by patients)

Instructions:

Please complete the following questions upon awakening for the day.

1a. Approximately what time did you start trying to fall asleep last night?

[Enter time: XX:XX PM/AM]

1b. Approximately what time did you fall asleep last night?

[Enter time: XX:XX PM/AM]

2. Approximately how many times did you wake up last night (not including when you woke up for the day today)? Record "0" if you do not remember waking up last night.

[Enter number of times: XX]

3. Considering all the times you woke up last night, how much time were you awake in total? Record "0" if you do not remember waking up last night.

[Enter total amount of time awake: XX hours and/or XX minutes]

4. At what time did you wake up for the day today?

[Enter time: XX:XX PM/AM]

5. Select the number that best describes how rested you felt when you got up for the day today.

0	1	2	3	4	5	6	7	8	9	10
Not at all rested										Very well rested

7. Peak Pruritus NRS (completed by patients)

On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No itch										Worst itch imaginable

8. Skin Pain NRS (completed by patients)

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?

0	1	2	3	4	5	6	7	8	6	10
No pain										Worst pain possible

9. Skin Burn NRS (completed by patients)

Think about all the areas of your skin with eczema. How much did your skin burn at its worst in the past 24 hours?

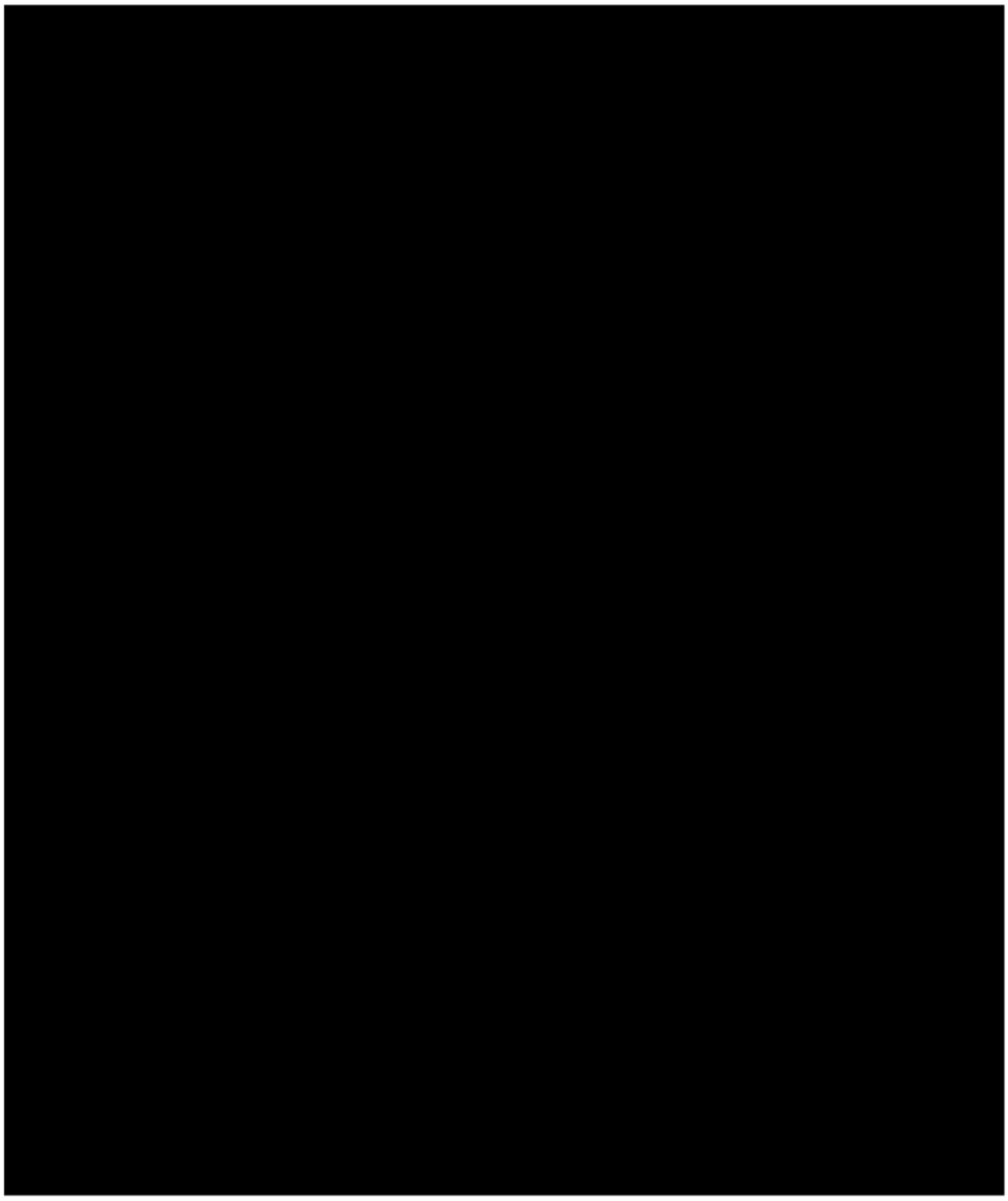
0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much

10. Skin Sensitivity to touch NRS (completed by patients)

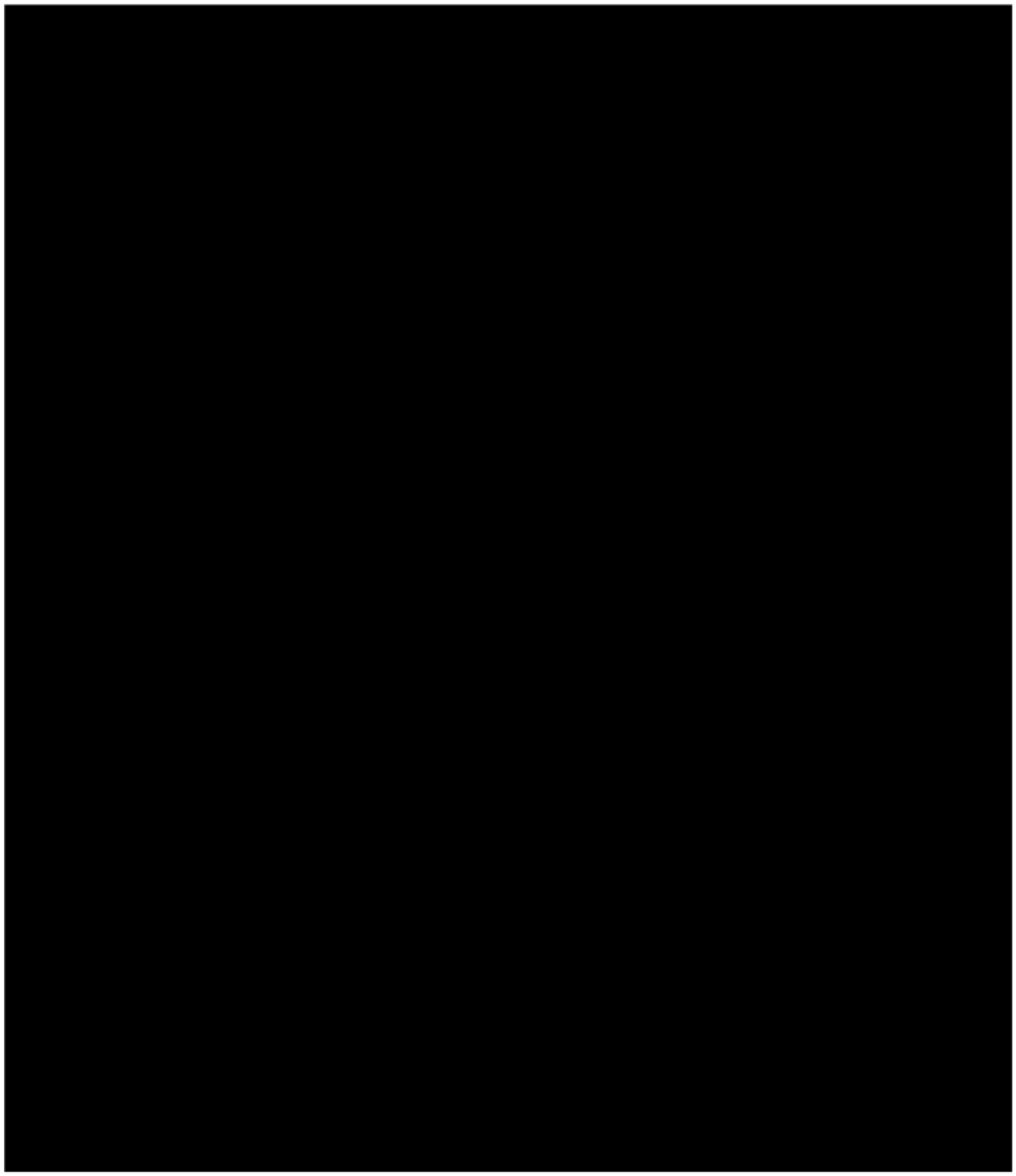
Think about all the areas of your skin with eczema. How sensitive was your skin at its worst in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Normal										Extremely sensitive

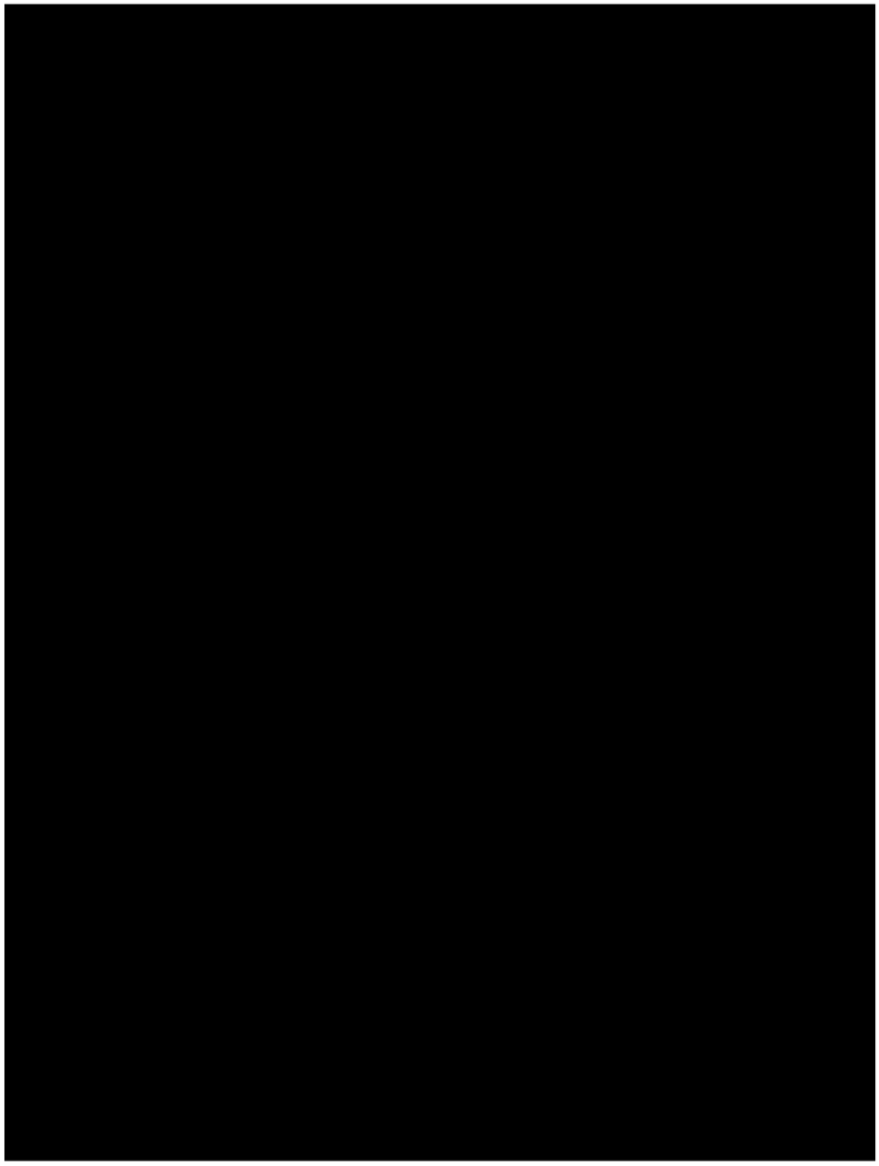
11. PROMIS Sleep Related Impairment-SF8a (completed by patients)

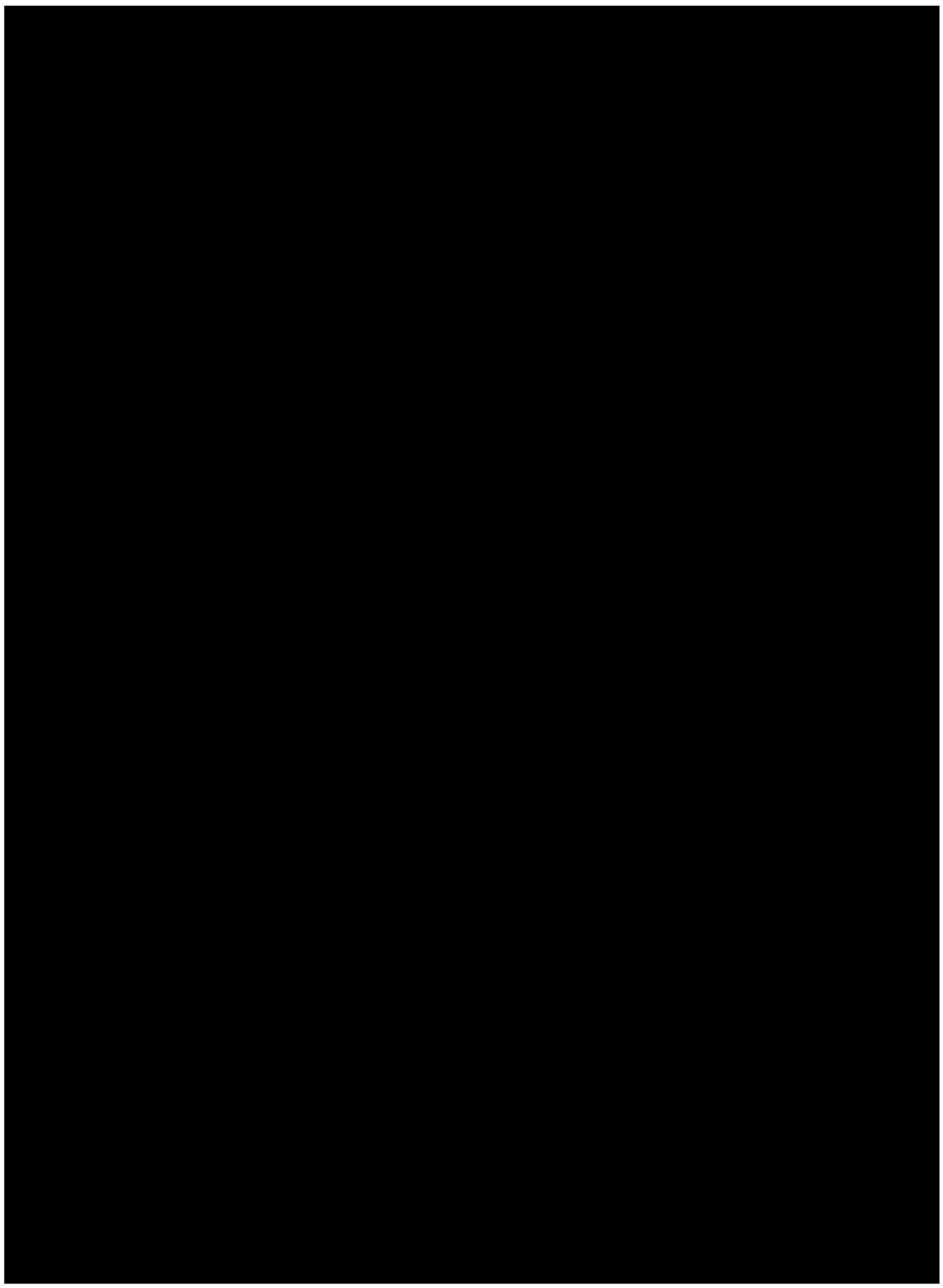


12. Epworth Sleepiness Scale (completed by patients)

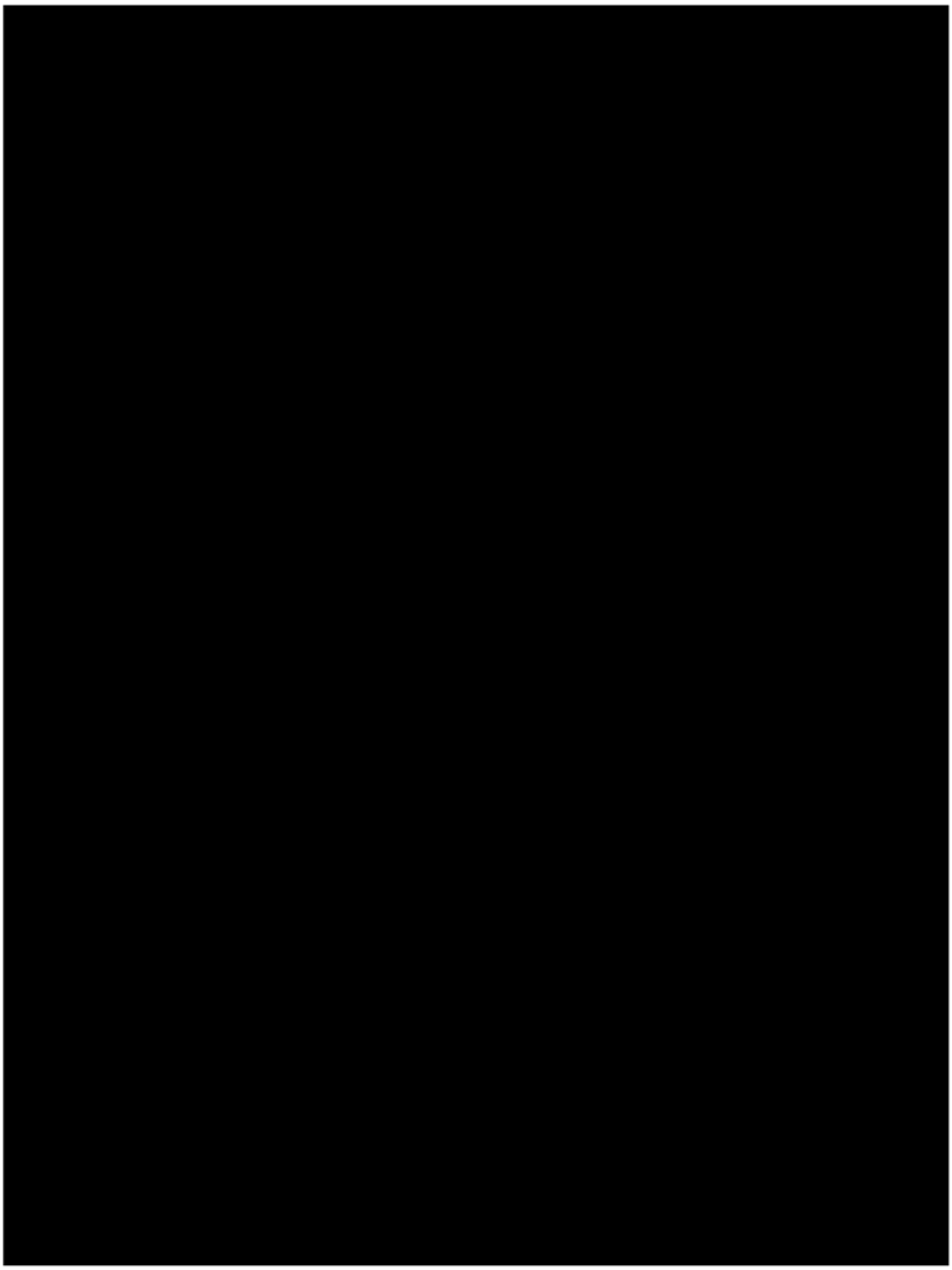


13. POEM (completed by patients)

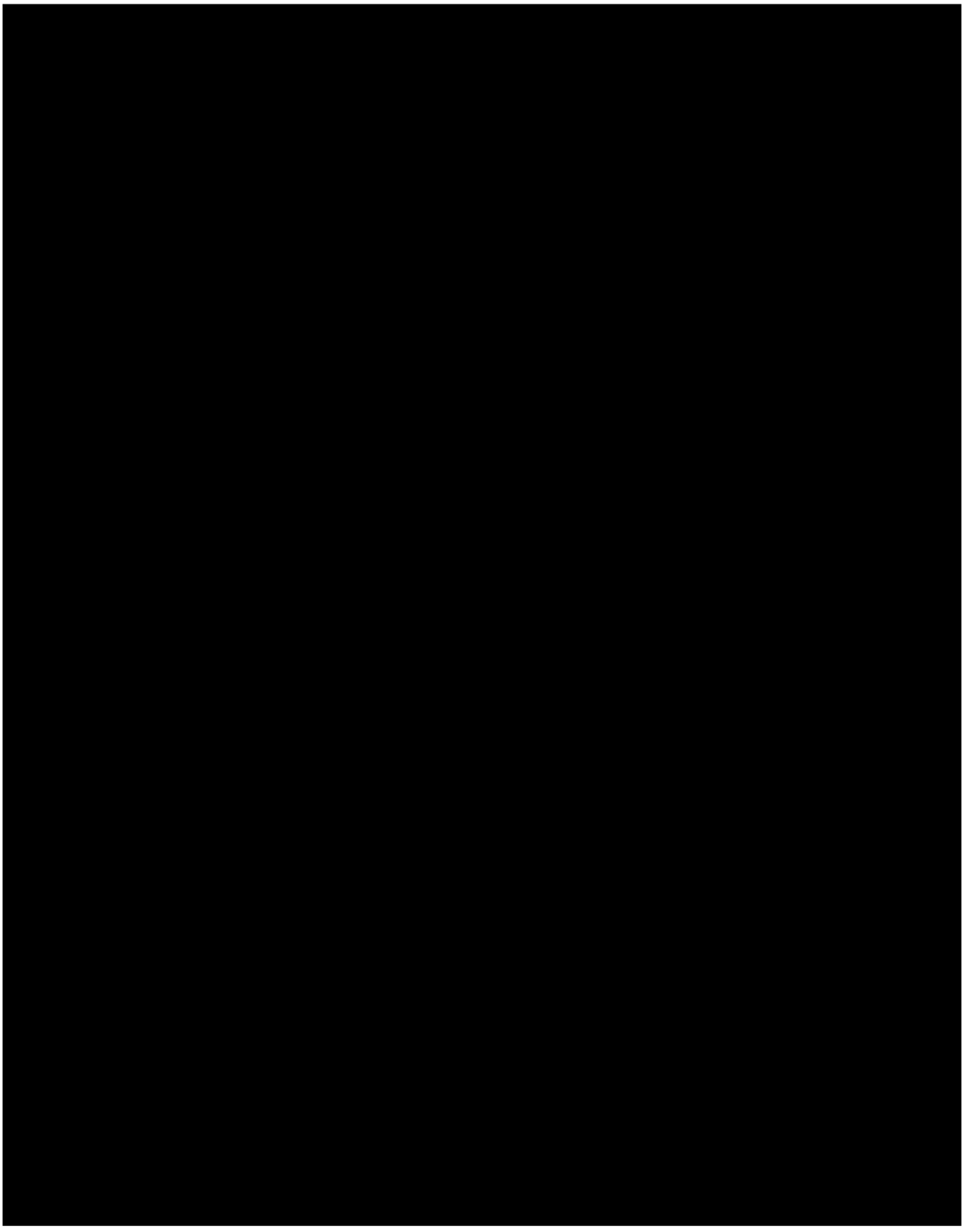




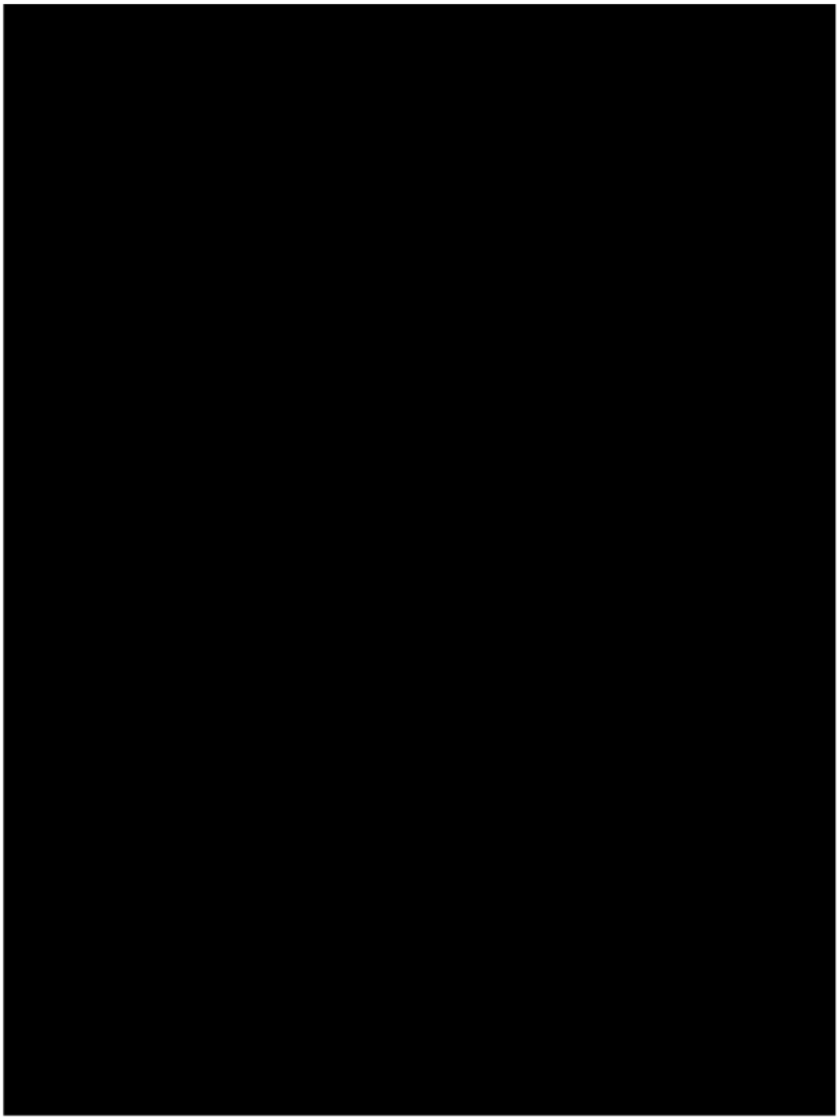
14. DLQI (completed by patients)

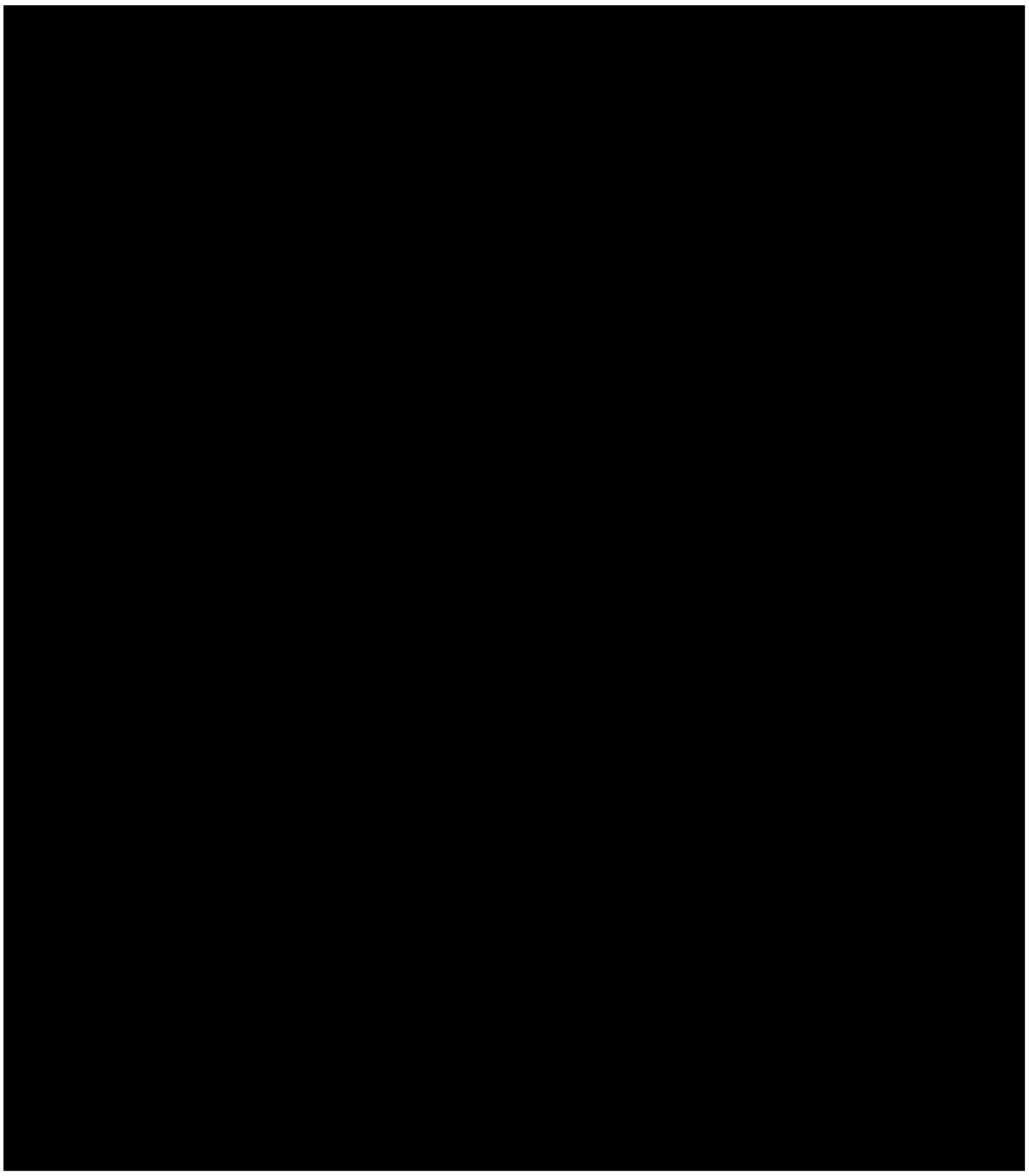


15. HADS (completed by patients)



16. ACQ-5 (completed by patients)





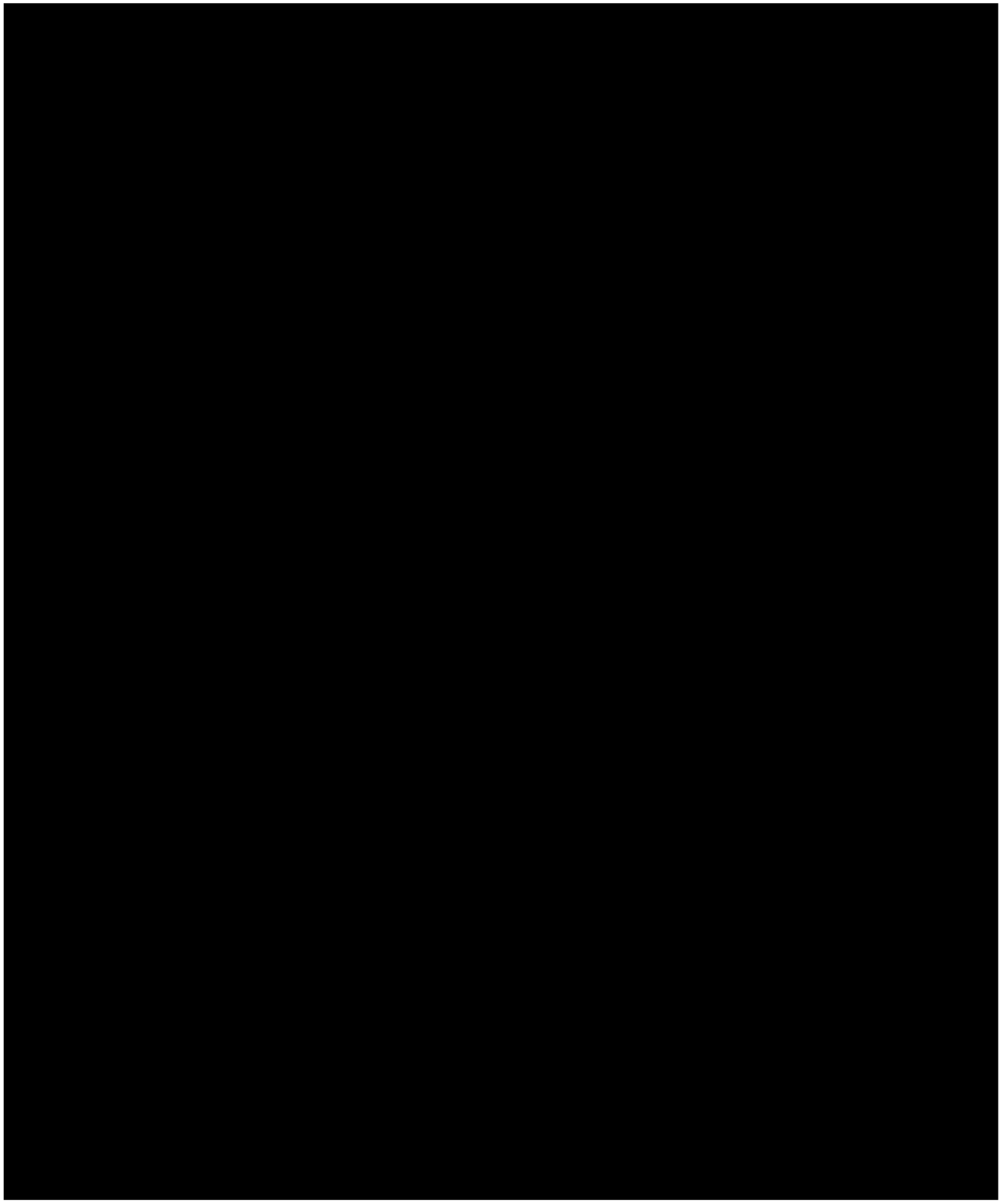
17. Allergic Rhinitis-Visual Analog Scale (AR-VAS) (completed by patients)

Instructions: Please place a vertical mark on the line below to indicate how bothersome are your allergic symptoms.

Overall, how much are your allergic symptoms bothering you today?

Not at all 10 cm Extremely bothersome

18. Work Productivity and Activity Impairment Questionnaire for AD (WPAI-AD) (completed by patients)



19. Work/School Days Missed

1. What has your employment status been since

   _____ ?
   (dd/mmm/yyyy)
   [insert the date of last assessment]

   - ☐ Employed and/or in school full time (≥4 days/week, cumulatively work + school)
   - ☐ Employed and/or in school part time (<4 days/week, cumulatively work + school)
   - ☐ Not employed (includes retired)/Not in school

For those employed (full time or part time)/students:

2. How many days have you missed from work/school because of your skin condition since

   _____ ?
   (dd/mmm/yyyy)
   [insert the date of last assessment]

   Specify: __ __ __ Days *(half days = 0.5 days)*

NOTES:

Assessment periods (i.e., time interval from the date of last assessment through the current date) must be contiguous. Leave no gaps. Cumulatively, these periods must cover the entire study duration.

Avoid duplicate reporting. If the patient missed work because of his/her skin condition on the day of assessment, this day should be recorded only once.

Record only days on which patient's skin condition prevented him/her to go to work. Otherwise, do not record the days on which the patient missed work only to participate in study visits.

10.10 APPENDIX 10: POLYSOMNOGRAPHY (PSG) SUB-STUDY

1. Introduction

Patients with AD are known to have significant sleep disorders due to scratching and perhaps other AD related pathophysiology. The overall objective of the current study is to evaluate the sleep quality of these AD patients treated with dupilumab, using sleep diary and actigraphy, and other patient reported assessments.

Within this study a PSG sub-study is planned for approximately 30 patients. Polysomnography is a multi-parametric test used in the study of sleep (eg, biophysiological changes that occur during sleep) and it is a standard diagnostic tool in sleep medicine. Polysomnography is typically performed at night, usually in a clinic. Sleep parameters that are commonly obtained during a PSG procedure will be collected for this study, mainly including sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), longest sleep episode, stages of sleep, sleep efficiency and arousal index.

The objective of the PSG sub-study is to evaluate the above sleep parameters with a more objective assessment tool to provide additional robust data in support of the diary and actigraphy evaluations.

2. Patients

Of the 201 participants, approximately 30 consenting patients (approximately 20 dupilumab and 10 placebo patients) will participate in this PSG sub-study.

Based on expert input, review of the limited literature and operational feasibility it is decided that a sample size of 30 patients could be sufficient to gather reliable PSG data to represent the whole study group. The PSG data from this group will not be used in statistical comparisons between dupilumab and placebo therefore no statistical considerations took place in deciding the subgroup size. Centers selected for the PSG sub-study are experts in sleep research and have ample experience with regard to PSG procedures and data collection/scoring. Selection of patients for the PSG sub-study will be based on proximity (where patients live) to participating sleep centers and availability for several overnight stays at the centers per study protocol.

3. Schedule

a) At Screening 2 Visit (Day -7), patients will be asked to keep a regular sleep/wake schedule through Day -1 (2nd PSG night) with approximately 30 to 60 minutes deviation from their usual bed time. The usual bedtime “Baseline” will be chosen by the patient and should reflect their habitual schedule. This sleep/wake schedule will be monitored using the sleep diary, which will begin on Screening 2. Patients will be reminded (reminder call/text) that the baseline study visit should be scheduled at least one week after travel for those patients who traveled across more than 1 time zone in order to record normal sleep/wake cycle.

b) Beginning on Study day 77 (1 week before the Primary Endpoint Visit, Visit 6) and continuing until after the third PSG night, patients will keep a regular sleep/wake

schedule with approximately 30 to 60 minutes deviation from their schedule chosen for the Baseline sleep schedule. During this reminder call/text patients will be asked if they plan to travel across more than one time zone in the next 7 days. If yes, their PSG and the accompanying site visit (visit 6) should be rescheduled so that there will be a minimum of 7 days between such travel and the PSG. The sleep/wake schedule will be monitored using sleep diary, which will begin on Screening 2 and continue past Visit 6. Polysomnography should occur at least one week after travel for those patients who traveled across more than 1 time zone.

4. Procedures

Before any PSG procedures, the site should calculate the mean of the sleep quality NRS and the mean of peak pruritus NRS completed for 5 days by the patient, to confirm that inclusion criteria 7 and 8 are met.

A) Day of admission

a) The sleep center staff will document all caffeine, tobacco, alcohol, and prescription or over the counter medications taken since awakening.

b) Patients to bring sleep diary (iPad) provided by the sponsor to the sleep center. This will be reviewed by study staff.

c) Patients to arrive at sleep center approximately 3 hours before their chosen sleep time.

d) Patients will wear actiwatch when arriving in the clinic.

e) Sleep center will do clinical admission per their SOPs.

f) Sleep center will administer electrodes per American Academy of Sleep Medicine (AASM) criteria for a clinical sleep recording, including electroencephalogram, electrooculography, electromyography, ECG, electrodes for monitoring leg movements, airflow sensors and Respiratory Inductance Plethysmography sensors for monitoring breathing and O_2 saturation. Calibrations per SOP for the sleep center.

g) Sleep center will begin sleep recording ~30 minutes prior to each individual patient's chosen sleep time.

h) Sleep center will begin a video recording ~30 minutes prior to each individual patient's chosen sleep time.

B) Next day (and the third PSG night)

a) Sleep recording will end after each individual patient's natural wake time.

b) Video recording will end after each individual patient's natural wake time.

c) Patients will continue to wear actiwatch and complete all patient reported outcomes in their iPad upon awakening for the day.

d) Patients and study site will complete the remaining study related assessments as per the schedule of activities.

C) Within 2 business days

a) Sleep center will send the EDF files or other agreed upon format of the PSG recordings to a blinded central reader site which will use AASM criteria to score by a registered PSG technician.

- Reported outcomes include (but not limited to) sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), longest sleep episode, stages of sleep, sleep efficiency and arousal index.

b) If a patient has evidence of a clinical sleep disorder as detected by the PSG, the central reading PSG clinic will notify the PSG site the patient is from, and the PSG site will then notify the patient. That site will also be responsible for reporting this as an AE if relevant (ie, in case of worsening of frequency or severity of sleep disorder as compared to baseline status). These patients will continue in the main study unless their condition requires immediate attention or permanent or temporary discontinuation of the study for any safety reason.

10.11 APPENDIX 11: PROTOCOL AMENDMENT HISTORY

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

Changes in protocol amendment 1 (dated 10-Oct-2019) are listed below.

Protocol amendment 1 summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Study acronym "DUPISTAD" has been added	To be consistent with Informed Consent Form
1.1 Synopsis: intervention groups and duration 1.3 Schedule of Activities 4.1 Overall design	Added that screening can be done as a single visit, if preferred by the patient and the investigator	For logistical reasons, to allow for some flexibility
1.1 Synopsis: Intervention groups and duration 1.3 Schedule of Activities 4.1 Overall Design 8.1.1.5 Polysomnography (sub-study; conducted by the trained professional)	Added the word "preferably" between 2 consecutive overnight PSGs	Minor edit to add flexibility for possibly non-consecutive nights, as feasibility showed it may not always be possible to have the 'acclimatization' visit and the actual assessment visit on consecutive nights.
1.1 Synopsis: Intervention groups and duration 4.1 Overall Design	Added "in selected US sites" for PSG	Minor edit to mention that PSG sub-study will be conducted in US sites (was already planned, but not specified in the original protocol).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis : Study Intervention Dose Regimen 6 Study Intervention Table 2 Overview of study interventions administered	Language modified from "last injection through week 24" to "last injection at week 22"	Already planned in the original protocol; language modified to make it more clear that the last injection within the 24-week treatment period will be at week 22.
1.3 Schedule of Activities	+1 day added to all other visits post Day 1	To correct a minor error in the SoA. As Baseline is at Day 1, one day was added to all visits post Day 1, to keep exactly 1 week (7 days), or 2 weeks (14 days), or 4 weeks (28 days) between further consecutive visits.
1.3 Schedule of Activities	Psychomotor Vigilance test (PVT) and Neurocognitive test (Automated Psychological Assessment Metrics-ANAM) split into 2 separate lines in the SoA table.	Minor (formatting) change, for clarity.
2.3 Benefit/Risk Assessment	Added summary of benefit and risk of dupilumab treatment	This section was reinserted as per EU Health Authorities request.
3.0 Objectives and Endpoints	Added specific details about procedural reaction time score along with running memory and mathematical processing in exploratory endpoint.	Corrected an omission from the previous version to match the clinical measurements with the corresponding endpoints.
5.2 Exclusion criteria E28	Contraception period after the last dose of study drug changed from 120 days to 12 weeks	This change is done to correct an error in the original protocol and make it consistent with IB and ICF, and is also based on dupilumab half-life.
9.4.1 Efficacy analysis Table 4 Efficacy analyses	MMRM does not employ formal imputation for missing data; therefore no imputations for missing values will be carried out for the primary analysis.	To correct an omission as per EU Health Authorities request, to clarify how missing data will be handled. Mixed Model Repeated Measures (MMRM) will implicitly account for missing values.
9.4.1 Efficacy analysis Table 4 Efficacy analyses	Added that formal statistical comparisons will not be performed on the PSG endpoints.	No change in the planned statistical analysis, but clarification added to explain that, due to the limited sample size of the sub-study, the analyses will be limited to providing summary statistics for the PSG endpoints.
Section 10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Removed bullet point stating that additional pregnancy testing is not required during the study period (treatment as well as follow-up)	Corrected a minor error in the previous version, to match with assessments as per SoA.
Section 10.10 Appendix 10 Polysomnography (PSG) sub-study	Added Appendix for polysomnography	The PSG Appendix is added in the protocol amendment to provide the detailed description, procedure, and schedule for polysomnography, as requested by EU Health Authorities.

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections) were implemented throughout the protocol.

11 REFERENCES

1. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol. 2012;130(6):1344-54.

2. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphoenotypes of asthma. Am J Respir Crit Care Med. 2009;180(5):388-95.

3. Bieber T. Mechanisms of disease: Atopic Dermatitis. N Engl J Med. 2008;358:1483-94.

4. Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet. 2013;381(9871):997-1020.

5. Silverberg JI. Associations between atopic dermatitis and other disorders. 2018;7(F1000 Faculty Rev):303.

6. Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep. 1997;20(4):267-77.

7. Jeon C, Yan D, Nakamura M, Sekhon S, Bhutani T, Liao W. Frequency and management of sleep disturbance in adults with atopic dermatitis. A systematic review. Dermatol Ther. (Heidelb) 2017;7(3):349-64.

8. Ruzicka T, Mihara R. Anti-interleukin-31 receptor A antibody for atopic dermatitis. N Engl J Med. 2017;376:826.

9. Charman CR, Venn AJ, Williams, HC. The patient-oriented eczema measure. Arch Dermatol. 2004;140:1513-19.

10. Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. Br J Dermatol. 1999;141(4):698-702.

11. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-70.

12. Herrmann C. International experiences with the hospital anxiety and depression scale – a review of validation data and clinical results. J Psychosom Res. 1997;42(1):17-41.

13. Basner M, Dinges, DF. Maximizing sensitivity of the Psychomotor Vigilance Test (PVT) to sleep loss. Sleep. 2011;34:581-91.

14. Wilken JA, Kane R, Sullivan CL, Wallin M, Usiskin JB, Quig ME, et al. The utility of computerized neuropsychological assessment of cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult Scler. 2003;9:119-27.

15. Reeves DL, Winter KP, Bleiberg J, Kane RL. ANAM® genogram: Historical perspectives, description, and current endeavors. Arch Clin Neuropsychol. 2007;22S:S15-S38.

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