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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DUPILUMAB IN ADULT AND ADOLESCENT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC HAND AND FOOT DERMATITIS

Compound:	Dupilumab
Study Name:	Liberty-AD-HAFT
Clinical Phase:	3
Protocol Number:	R668-AD-1924
Protocol Version	R668-AD-1924 Amendment 2
Amendment 2 Date of Issue:	*See appended electronic signature page*
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Medical/Study Director:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACD	Allergic contact dermatitis
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BL	Baseline
BSA	Body Surface Area
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EASI	Eczema Area and Severity Index
EC	Ethics Committee
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HECSI	Hand eczema severity index
HFD	Hand and foot dermatitis
Hep C Ab	Hepatitis C antibody
HIV	Human immunodeficiency virus
ICD	Irritant contact dermatitis
ICDRG	International Contact Dermatitis Research Group
ICF	Informed consent form
ICH	International Council for Harmonisation
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4Rα	IL-4 receptor alpha subunit
IRB	Institutional Review Board
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System

JAK	Janus kinase
mTLSS	Modified Total Lesion Sign Score
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NRS	Numerical Rating Scale
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PPS	Per protocol set
PUVA	Psoralen and UVA
PV	Phone visit
QoL	Quality of life
QOLHEQ	Quality of Life in Hand Eczema Questionnaire
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TRUE	Thin Layer Rapid Use Epicutaneous
UVB	Ultraviolet B
WBC	White blood cell
WPAI+CIQ	Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire
WPCBP	Women of childbearing potential

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AMENDMENT HISTORY

Amendment 2

The key changes implemented in this protocol amendment are a) Modification of the instrument used in assessment of primary endpoint (Investigator Global Assessment [IGA] for hands and feet) and b) Revision of the patch test series to be used to exclude patients with Allergic Contact Dermatitis (ACD).

The following table outlines the changes made to the protocol and the affected sections:

Description of Change	Brief Rationale	Section Number and Name
IGA Instrument		
Modified the IGA for hands and feet instrument. Major changes made to the IGA instrument were as follows: • Consistent with atopic dermatitis (AD) trials in the dupilumab program, the revised IGA instrument now will be based on an **overall** impression of disease severity of the hands and feet (rather than assessment of disease severity of **individual** hand and foot separately). The investigator will be asked to assign a single score to reflect this clinical judgment (rather than rating each individual hand and foot separately to assign four separate IGA scores). • The IGA score has been de-coupled from the Modified Total Lesion Sign Score (mTLSS). The IGA score will now be based on a **clinical** assessment rather than an **auto-calculation** based upon mTLSS score. • Multiple permutations for different IGA severity levels have been removed. Each IGA severity is associated with defined morphological descriptors to enable clinical interpretability.	In response to comments from a health authority which had requested that the IGA be a clinical assessment of overall disease severity of hands and feet and be easy to interpret clinically.	Appendix 2 Investigator Global Assessment for Hand and Foot Atopic Dermatitis Appendix 3 mTLSS Modified Total Lesion Sign Score for Hand and Foot Atopic Dermatitis (added) Section 7.2.1 Inclusion Criteria, #3 and #4 Section 9.2.2.2 Modified Total Lesion Sign Score for Hands and Feet

Description of Change	Brief Rationale	Section Number and Name
Inclusion Criteria #3 and #4 (related to disease severity and IGA score) were revised accordingly to reflect the modified IGA scoring methodology.		
Patch Test		
Patch test series to be used in the study during screening period to exclude patients with ACD were changed as follows: • In the US, the American Contact Dermatitis Society (ACDS) core allergen series was changed to the TRUE (Thin layer Rapid Use Epicutaneous) test. • In the EU, the European Baseline Series (EBS) was changed to the TRUE test along with an additional panel of allergens which are missing in the TRUE test but are commonly implicated in causing ACD of hands and feet. • In Japan, the patch test panel was changed from the Japan standard series to the patch test panel (S).	To use an allergen series which is approved by regulatory agencies in the corresponding geographical regions.	Clinical Study Protocol Synopsis, Study Design Section 9.2.1.1 Patch Testing
Updated the statistical power from >90% to >85% based on the revised assumption for treatment effect.	The approved TRUE test has fewer number of allergens than a broader allergen panel such as ACDS, which is currently unapproved in the US. The TRUE test has been reported to miss approximately 33% of cases with ACD that are detected by ACDS. With the use of the TRUE test there is a risk that patients with ACD will be enrolled in this trial. Based on the currently available clinical and scientific evidence, dupilumab is not expected to be effective in this patient group.	Clinical Study Protocol Synopsis, Statistical Plan Section 11.2 Justification of Sample Size

Description of Change	Brief Rationale	Section Number and Name
	Accordingly, the assumption for treatment effect was lowered for the enrolled population, therefore, the power calculation was updated.	
Changes Related to Stratification Factors		
Clarified that the number of adult patients will be capped at approximately 100 to ensure that, at a minimum, approximately 30 adolescents will be enrolled.	In response to comments from a health authority.	Clinical Study Protocol Synopsis, Sample Size Section 6 Study Design Figure 1 Study Flow Diagram Section 7.1 Number of Patients Planned Section 8.6 Method of Treatment Assignment
Removed randomization stratification factor for presence of AD lesions outside hands and/or feet (yes/no).	In response to comments from a health authority to limit the number of stratification factors to reduce the risk of having cells with small frequencies within strata. This decision was supported by further discussions with external experts who concluded that of the various stratification factors specified in the protocol, this one factor was least likely to influence response to treatment.	Clinical Study Protocol Synopsis, Statistical Plan: Analysis Methods Section 3.2.1 Rationale for Study Design Figure 1 Study Flow Diagram Section 6.1 Study Description and Duration Section 8.6 Method of Treatment Assignment Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
Specified the stratification factor of geographic region is United States versus Japan versus other countries.	In response to a health authority request.	Clinical Study Protocol Synopsis, Statistical Plan: Analysis Methods Section 3.2.1 Rationale for Study Design Figure 1 Study Flow Diagram Section 6.1 Study Description and Duration

Description of Change	Brief Rationale	Section Number and Name
		Section 8.6 Method of Treatment Assignment Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
Changes Related to Endpoints		
In the Secondary Endpoints for Efficacy, moved the peak Pruritus NRS-related endpoints to before the mTLSS-related endpoint.	To highlight the importance of pruritus endpoints, as pruritus is the most important symptom from a patient perspective.	Clinical Study Protocol Synopsis, Secondary Endpoints for Efficacy Section 8.4.2 Secondary Endpoints
Proportion of patients with NRS 4-point reduction from baseline to week 16 was promoted to key secondary endpoint.	To highlight the importance of pruritus as a major symptom in hand and foot AD which is highly correlated with patient quality of life. A reduction in 4 points has previously been established as a clinically relevant change in patients with AD.	Clinical Study Protocol Synopsis, Secondary Endpoints for Efficacy Section 4.1.2 Secondary Endpoints Section 11.4.3.2 Secondary Efficacy Analyses
Changes to Statistical Analysis Plan		
Removed description of unblinded primary analysis of the study from Section 6.2 Planned Interim Analysis, as the primary analysis is not an interim analysis and the description already exists in Section 11.5. Changed Section 11.5 heading from "Interim Analysis" to "Timing and Operational Considerations of Statistical Analyses" as there is no interim analysis.	For consistency and clarity.	Section 6.2 Planned Interim Analysis Section 11.5 Timing and Operational Considerations of Statistical Analyses (revised heading)
Specified important protocol deviations that will exclude patients from the per protocol set (PPS).	In response to a health authority request.	Clinical Study Protocol Synopsis, Statistical Plan: Efficacy Analysis Sets Section 11.3.1 Efficacy Analysis Sets

Description of Change	Brief Rationale	Section Number and Name
Added primary estimand definition for the primary and key secondary efficacy endpoints based on ICH E9 (R1)	To be compliant with ICH E9 (R1).	Section 11.4.3.1 Primary Efficacy Analysis Table 2 Summary of Primary Estimand for Primary Endpoint (added) Section 11.4.3.2 Secondary Efficacy Analysis Table 3 Summary of Primary Estimand for Key Secondary Endpoint (added)
Removal of Assessments		
Removed the following assessments from the protocol: Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), Hospital Anxiety and Depression Scale (HADS), Patient Oriented Eczema Measure (POEM), ophthalmological examination, body surface area (BSA) involvement of AD, thymus and activation-regulated chemokine (TARC), lactate dehydrogenase (LDH), immunoglobulin E (IgE), optional RNA sample, and research samples (serum/plasma). The frequency of vital signs, clinical laboratory, PK, and ADA assessments was decreased.	To reduce patient burden and improve overall compliance with study procedures/assessments.	Clinical Study Protocol Synopsis, Objectives, Endpoints, Procedures and Assessments Section 2.2 Secondary Objectives Section 4.1.2 Secondary Endpoints Section 5.2 Efficacy Variables Section 5.5 Pharmacodynamic and Other Biomarker Variables Section 8.7 Blinding Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, #11, #19, and #28 deleted, and #3, #4, #14, #21, and #22 revised. Footnotes were renumbered. Section 9.2.2.7 Dermatology Life Quality Index (deleted) Section 9.2.2.10 Hospital Anxiety and Depression Scale (deleted) Section 9.2.2.13 Patient Oriented Eczema Measure (deleted)

Description of Change	Brief Rationale	Section Number and Name
		Section 9.2.2.16 Body Surface Area Involvement of Atopic Dermatitis (deleted) Section 9.2.3.5 Ophthalmological Examination (deleted) Section 9.2.6 . Pharmacodynamic and Exploratory Biomarker Procedures Section 9.2.7.1 Pharmacogenomic Analysis (Optional) Section 11.4.8 Analysis of Pharmacodynamic and Exploratory Biomarker Data (deleted) Section 19 References
COVID-related Changes		
Added footnote * for In-Clinic Visits and footnote ** for Laboratory Testing in the Schedule of Events table, and revised footnote #15 (which became #14 with this amendment) to indicate the following, respectively, in case of lack of availability of site staff and/or patients to come to site for in-clinic visits due to COVID-19 pandemic: • Phone visits/virtual visits/telemedicine visits/home visits by skilled staff should be considered for conducting certain assessments. • Alternate measures may be used for clinical lab testing. • The sponsor may implement processes for direct-to-patient shipment of study drug.	To mitigate the risk to patient safety and data integrity resulting from COVID-19 restrictions/lockdowns.	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, footnote * added, footnote ** added, footnote #15 (which became #14) revised

Description of Change	Brief Rationale	Section Number and Name
Changes Made for Completeness and Clarity		
The definition of patient population was corrected to make it consistent with the eligibility criteria by changing 'high potency' to 'medium-to-high potency' TCS, which now reads: "The proposed study population is patients with chronic, moderate-to-severe hand and foot AD inadequately responsive to medium-to-high-potency TCS or in whom medium-to-high-potency TCS are inadvisable."	The study population was always intended to be patients with chronic, moderate-to-severe hand and foot AD inadequately responsive to medium-to-high-potency TCS from the beginning. The words 'medium to' were **inadvertently** left out in the previous version of the protocol in the study population section, although the eligibility criteria did specify medium-to-high-potency TCS.	Clinical Study Protocol Synopsis, Population: Target Population Section 7.2 Study Population
Added UVB to the list of treatments that require a 4-week washout period prior to the patch testing. Added localized PUVA or narrow band UVB on hands and/or feet to the list of prohibited medications.	For completeness and clarity.	Section 7.2.2 Exclusion Criteria, #6c Section 8.10.1 Prohibited Medications and Procedures Section 9.2.1.1 Patch Testing
Added topical and systemic JAK inhibitors to prohibited medications.	For completeness and clarity.	Section 7.2.2 Exclusion Criteria, #8 Section 8.3 Rescue Treatment Section 8.10.1 Prohibited Medications and Procedures Section 9.2.1.1 Patch Testing
Added that latex should be avoided.	For completeness and clarity.	Section 8.10.3 Skin Protection Measures
Corrected footnote designation in the Schedule of Events for "Optional DNA, RNA sample" from #3 to #4. Separated the "Optional DNA and RNA sample" into 2 separate rows.	Correction of a typo.	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events
Added eCOA instruments, eDiaries, and tablet devices for	For completeness.	Section 12.1.2 Electronic Systems

Description of Change	Brief Rationale	Section Number and Name
collecting/recording some of the efficacy assessment data.		

Amendment 1

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Added information regarding the "Coronavirus Disease 2019" (COVID-19) pandemic and its impact on clinical trials.	Section 3.3 Risk-Benefit Section 9.1 Schedule of Events Section 11 Statistical Plan
Details were added regarding injection sites.	Section 8.1 Investigational and Reference Treatments
Added instruments for IGA and Modified Total Lesion Sign Score (mTLSS). These instruments incorporate the written feedback received from a health authority.	Section 9.2.2.1 Investigator Global Assessment of Hand and Foot Section 9.2.2.2 Modified Total Lesion Sign Score for Hands and Feet Appendix 2 Modified Total Lesion Sign Score and Investigator Global Assessment
Added statement that a responder threshold (currently unknown) for mTLSS in the study population will be determined using data gathered from this study. Analyses using this responder threshold will be conducted to help interpretation of the prespecified endpoints for the mTLSS. The methodology to be used for determining this responder threshold and the analyses will be specified in the SAP.	Section 9.2.2.2 Modified Total Lesion Sign Score for Hands and Feet
Added major criteria for the Hanifin and Rajka Diagnostic Criteria for AD.	Appendix 1 Hanifin and Rajka Diagnostic Criteria for Atopic Dermatitis- Major and Minor Criteria

Change	Section Changed
Removed randomization stratification factor for disease morphology and added stratification for geographic region (pooled countries set by interactive voice response system/interactive web response system [IVRS/IWRS]). Sub-group analysis for treatment effect in patients with hands only involvement vs involvement of hands and feet or feet only were requested by the health authority. The number of patients with hands only involvement will be capped at approximately 100. In parallel, the stratification factor for disease morphology was removed to limit the total number of factors. On further discussions with external experts, it was felt that disease morphology should not impact response to treatment with study drug. Furthermore, data from a prospective observational study with dupilumab in patients with AD of hands suggests that disease morphology does not impact response to treatment.	Clinical Study Protocol Synopsis: Population, Statistical Plans Section 3.2.1 Rationale for Study Design Section 6 Study Design Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 7.1 Number of Patients Planned Section 8.6 Method of Treatment Assignment Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis

Change	Section Changed
Changed inclusion criterion #2 to: Patients with chronic hand and/or foot dermatitis diagnosed at least 3 years prior to the screening visit for patients ≥18 years old and at least 1 year prior to the screening visit for patients 12 to <18 years old. Previously, this criterion was: Patients with chronic hand and/or foot dermatitis diagnosed at least 6 months prior to the screening visit. This modification will ensure that the disease duration to define chronicity is consistent with that used in the dupilumab phase 3 global AD trials and allow sufficient time to demonstrate inadequate response to the current standard-of-care (topical corticosteroids) for hand and foot dermatitis. Added inclusion criteria: Patients with involvement of at least 2 anatomical areas with moderate to severe disease (IGA score of 3 or 4, separately for 2 anatomical areas) at screening and baseline (both hands, one hand and one foot, or both feet) AND Patients need to have an overall IGA hand and foot or hand or foot score of 3 or 4 at screening and baseline. This will ensure that patients will have extent of disease that is sufficient to justify treatment with a biologic. Added clarification to criterion #5 regarding inadequate AD treatment response to topical medications. Added inclusion criterion #9: Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit.	Section 7.2.1 Inclusion Criteria, #2, #3, #4, #5, #9

Change	Section Changed
Added a note that patients with a documented diagnosis of allergic contact dermatitis of hands and/or feet, who have a positive patch test reaction at screening will also be excluded from the study, regardless of whether history of current skin exposure to products containing this allergen (current relevance) is present. Previously, only patients with a clinically relevant positive patch test were excluded from the trial; clinical relevance to positive patch testing was based upon reporting of exposure to allergen by the patient. However, patients might not be able to recall such exposure leading to failure to exclude patients whose hand and foot dermatitis is caused by allergic contact dermatitis, rather than AD. Added exclusion criterion: Patients with a known diagnosis of protein contact dermatitis of hands and/or feet. These are patients with occupational or non-occupational contact to proteins such as food (eg, wheat, milk, fish), latex etc. with positive prick test who present with lesions of contact urticaria or dermatitis on hands/feet. Patients with protein contact dermatitis are spelled out separately from the broad group of allergic contact dermatitis as these patients typically have a negative patch test. Patients with protein contact dermatitis are not expected to benefit from the study drug based upon the available scientific and clinical evidence. The study population has been limited to patients with AD of hand and foot. For clarification, combined exclusion criteria #s 2 and 3 regarding exposure to irritants. Added guidelines to be used in screening to evaluate patient exposure to irritants.	Section 7.2.2 Exclusion Criteria, #1, #2, #3, #4, #13

Change	Section Changed
Added further text to skin protection measures. Added a row 'skin protection measures' to the Schedule of events. Also added the following inclusion criterion: Patients need to have been compliant with the skin protection measures (as outlined in Section 8.10.3) through the entire duration of the screening period (minimum of 4 weeks but lasting to a maximum of 8 weeks). This includes avoidance of irritants that are identified as causing exacerbation of hand and foot AD. These additions will ensure that patients whose disease can be managed by simple skin protection measures are not un-necessarily enrolled in a clinical trial with a biologic. Moreover, compliance with these skin protection procedures throughout the duration of the trial will prevent confounding of effect of study drug.	Section 7.2.1 Inclusion Criteria, #12 Section 6.1 Study Description and Duration Section 8.10.3 Skin Protection Measures Table 1 Schedule of Events
Reduced the frequency of assessments for patient-reported outcome measures to reduce patient burden and increase compliance. Added rows for 'assign disease morphology' and 'assign anatomical area of involvement' to the Schedule of Events as these were inadvertently omitted in the original protocol. Added footnotes to provide details for these assessments.	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, #9, #10
Added a sentence in protocol and corresponding row in the Schedule of Events that detailed history of exposure to irritants in occupational as well as non-occupational setting will be elicited to rule out irritant hand and foot dermatitis. This will lead to informed avoidance of such irritants during the screening period and will ensure that patients whose disease can be managed by simply avoiding irritants are not un-necessarily enrolled in a clinical trial with a biologic.	Table 1 Schedule of Events Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit

Change	Section Changed
Added a window for the second reading for patch test: day 3-day 7 assessment (previously only allowed at day 4). This will provide more flexibility to sites to schedule in-patient clinic visits as per patient convenience. Removed the extended European baseline series for contact allergens for patch testing and changed it to the European baseline series as the testing concentration for certain allergens in extended EU baseline series has not been finalized. Removed North American Contact Dermatitis Group (NACDG) patch test series. as the sponsor is having difficulty in sourcing this patch test series. A Japan specific patch test series (Patch test panel S) was added. Added the Australian baseline series in Australia.	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, #7 Section 9.2.1.1 Patch Testing
Removed Pruritus Categorical Scale to reduce patient burden.	Section 9.2.2.4 Hand and Foot Pruritus Categorical Scale – section removed from protocol body
Added Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire (WPAI+CIQ) and removed the assessment of missed work/school days.	Clinical Study Protocol Synopsis: Endpoints, Study Procedures and Assessments Section 4.1.2 Secondary Endpoints Section 5.2 Efficacy Variables Table 1 Schedule of Events Section 9.2.2.19 Work Productivity and Activity Impairment Plus Classroom Impairment Questions Section 9.2.2.11 Assessment of Missed Work/School Days – section removed from protocol body

Change	Section Changed
Made the following clarifications: • Details were added regarding moisturizers. • Specified that data from patients who receive rescue treatment as per adjudication during the study will be treated for efficacy analysis purposes as outlined in Section 11.4.3. • Clarified criteria for temporary discontinuation to ALT or AST >3 times ULN. • Clarified in the Schedule of Events and procedures that vital signs at baseline week 2 and week 4 will be done additionally at 30 minutes post-injection. • Added details regarding research samples and future biomedical research (FBR) samples. • Changed heart rate to pulse rate under vital signs assessment. • Removed alcohol and drug screens. • Changed Patient Global Assessment of Disease (PGAD) to Patient Global Impression of Severity (PGIS) and Patient Global Assessment of Treatment (PGAT) to Patient Global Impression of Change (PGIC) and corrected the description to make it specific for hand and foot AD. • Added sections to describe the Patient Oriented Eczema Measure (POEM) and Body Surface Area (BSA) involvement of AD to match assessments in the Schedule of Events. • Specified that the Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) will only be performed in patients who have AD lesions outside their hands and feet.	Clinical Study Protocol Synopsis: Procedures and Assessments Section 8.2 Background Treatment Section 8.3 Rescue Treatment Section 8.4.2.2 Reasons for Temporary Discontinuation of Study Drug Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, #11, #21, and #28 Section 9.2.2.7 Patient Global Impression of Severity Section 9.2.2.8 Patient Global Impression of Change Section 9.2.2.10 Quality of Life in Hand Eczema Questionnaire Section 9.2.2.13 Patient Oriented Eczema Measure Section 9.2.2.14 Eczema Area and Severity Index Section 9.2.2.15 Investigator's Global Assessment Section 9.2.2.16 Body Surface Area Involvement of AD Section 9.2.3.1 Vital Signs Section 9.2.3.4 Laboratory Testing
Corrected minor typographical and formatting issues.	Throughout protocol.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Moderate-to-Severe Atopic Hand and Foot Dermatitis
Site Locations	This is a global, multicenter study.
Principal Investigator	To be determined
Objectives	**The primary objective** of the study is to assess the efficacy of dupilumab on skin lesions in patients with atopic hand and foot dermatitis. **The secondary objectives** of the study are: • To assess the efficacy of dupilumab on various other domains (pruritus, pain, sleep loss, health related quality of life (QoL), work life impairment) in patients with atopic hand and foot dermatitis • To evaluate the safety and tolerability of dupilumab administered to patients with atopic hand and foot dermatitis • To evaluate systemic exposure and immunogenicity of dupilumab in patients with atopic hand and foot dermatitis **The exploratory objectives** of the study are: • To study dupilumab's mechanism of action (related to efficacy and/or safety), why some patients respond better than others (safety and/or efficacy), IL4R pathway, atopic hand and foot dermatitis and related diseases • To assess the concordance between treatment effect of dupilumab on a) atopic hand and foot dermatitis lesions and b) concomitant AD lesions on other parts of the body • To evaluate exposure-response relationships
Study Design	This is a global, multicenter, randomized, double-blind, parallel-group, placebo-controlled study investigating the efficacy and safety of dupilumab monotherapy in adult and adolescent patients with moderate-to-severe atopic hand and foot dermatitis as defined by a specific Investigator Global Assessment (IGA) assessment focused on these areas of the body. Eligible patients must have a documented history of inadequate response or intolerance to treatment of hand and foot dermatitis with topical AD medications. At the screening visit, adult patients will provide informed consent before any other study procedures are conducted. For adolescent patients, parents or legal guardians will provide informed consent and the patients will provide assent. After providing informed consent/assent, the patients will

be assessed for study eligibility at the screening visit. During the screening period, systemic treatments for AD will be washed out, as applicable, according to the eligibility requirements. Topical treatments for AD of hands and feet will also be washed out, according to the eligibility requirements. However, patients will be allowed to use topical treatments for treatment of AD on other parts of the body with certain restrictions.

Patients may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure is related to failing the disease severity inclusion criteria.

Patch testing with a standard series of allergens will also be carried out during the screening period to exclude patients with predominantly allergic contact dermatitis (ACD) of hand and foot. The standard series used will vary based upon the region of conduct of the study. Examples of the country-specific series based on countries the study is conducted include TRUE test for US, TRUE test and an additional panel of allergens which are missing in TRUE test but are commonly implicated in causing ACD of hands and feet for patients in the EU, and patch test panel (S) for Japan. Patients will need to be discontinued from topical/systemic medications for AD prior to the patch testing.

Patients who meet the eligibility criteria will be randomized (1:1) to dupilumab subcutaneously (SC) every 2 weeks (Q2W) or matching placebo (see details of dosing regimens in the Treatments section).

During the treatment period, patients will have in-clinic visits at week 2 and week 4, and then in-clinic visits every 4 weeks (Q4W) through week 16 with bi-weekly phone visits in between the in-clinic visits. Patients and/or parents/caregivers will be trained on injecting study drug during in-clinic visit 2 (day 1) to visit 6 (week 4). During weeks in which no in-clinic visit is scheduled, patients will either self-inject study drug or the parent/caregiver will administer study drug to the patient. In case patients do not want to self-inject and the parents/caregivers do not want to administer study drug to patient, patients may have the clinic staff administer all the study drug injections in the clinic. Safety laboratory tests, collection of samples for study drug concentrations and immunogenicity, and clinical assessments will be performed at specified clinic visits.

The end of treatment visit will occur at week 16, 2 weeks after the last dose of study drug. The primary endpoint will be assessed at this visit. If patients prematurely discontinue study drug, the patients will be encouraged to stay in the study to have data collected at all remaining scheduled visits until completion of the planned end of study visit.

Post-treatment follow-up period: Upon completing the 16-weeks randomized treatment period, patients will enter a 12-week follow-up period. The end of study visit will occur at week 28.

Study Duration	The duration of the study for each patient is approximately 28 weeks, excluding the screening period.
End of Study Definition	The end of study is defined as the date of the last visit of the last patient in the study.
Population	
Sample Size:	Approximately 130 patients (65 patients per arm) will be enrolled at approximately 50 global sites. The number of adult patients will be capped at approximately 100 to ensure that, at a minimum, approximately 30 adolescents will be enrolled. The number of patients with hands only involvement will be capped at approximately 100.
Target Population:	The proposed study population is patients with chronic, moderate-to-severe atopic hand and foot dermatitis inadequately responsive to medium-to-high-potency topical corticosteroids (TCS) or in whom medium-to-high-potency TCS are inadvisable. Only patients meeting the diagnostic criteria for AD will be included in this study. Patients with a confirmed diagnosis of irritant contact dermatitis or ACD as the predominant cause of hand and foot dermatitis will be excluded from the study.
Treatments	
Study Drug **Dose/Route/Schedule:**	• Dupilumab, administered SC Q2W – In adults: dupilumab 300 mg, after a loading dose of 600 mg on day 1, irrespective of body weight – In adolescents: Body weight ≥60 kg, dupilumab 300 mg, after a loading dose of 600 mg on day 1, body weight <60 kg, dupilumab 200 mg, after a loading dose of 400 mg on day 1
Placebo **Route/Schedule:**	• Matching placebo, administered SC Q2W
Endpoints	
Primary:	• Proportion of patients achieving an IGA (hand and foot) score of 0 or 1 at week 16
Secondary:	**Key Secondary Endpoint for Efficacy:** • Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥4 from baseline to week 16

Secondary Endpoints for Efficacy:

- Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus Numeric Rating Scale (NRS) ≥3 from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily hand and foot peak Pruritus NRS
- Percent change in Modified Total Lesion Sign Score (mTLSS) for hand/foot lesions from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily hand and foot peak Pain NRS
- Percent change from baseline to week 16 in weekly average of daily Sleep NRS
- Change from baseline to week 16 in percent surface area of hand and foot involvement with AD
- Percent change from baseline to week 4 in weekly average of daily hand and foot peak Pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥4 from baseline to week 4
- For patients with hand dermatitis, percent change from baseline to week 16 in Hand Eczema Severity Index (HECSI) score
- For patients with hand dermatitis, proportion of patients with HECSI-75 at week 16
- For patients with hand dermatitis, proportion of patients with HECSI-50 at week 16
- For patients with hand dermatitis, proportion of patients with HECSI-90 at week 16
- For patients with hand dermatitis, change from baseline to week 16 in Quality of Life in Hand Eczema Questionnaire (QOLHEQ)
- Change from baseline to week 16 in Work Productivity and Impairment (WPAI) and Classroom Impairment Questionnaire (CIQ)

Secondary Endpoints for Safety:

- Incidence of treatment-emergent adverse events (TEAEs) through week 16

Secondary Endpoints for Clinical Pharmacology and Immunogenicity:

- Trough concentration of functional dupilumab in serum at various time points

	• Incidence of treatment-emergent anti-drug antibodies (ADA) over time
Procedures and Assessments	Efficacy will be assessed during the study at specified clinic visits using patient reported assessments (including Daily hand and foot peak Pruritus NRS, Daily hand and foot peak Pain NRS, Daily Sleep NRS, QOLHEQ, Patient Global Impression of Severity [PGIS], Patient Global Impression of Change [PGIC], EQ-5D, WPAI+CIQ) and investigator-reported assessments (including IGA for hands and feet, mTLSS, percent surface area of hand and foot involvement with AD, HECSI, IGA [global], and Eczema Area and Severity Index [EASI]). Safety will be assessed by vital signs, physical examinations, clinical laboratory tests, and clinical evaluations. Patients will be asked to monitor all adverse events (AEs) experienced from the time of informed consent/assent until their last study visit. Laboratory testing will include hematology, blood chemistry, urinalysis, pregnancy testing, human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C antibody (Hep C Ab), tuberculosis (TB), DNA. Samples for drug concentration and ADA assay will be collected.
Statistical Plan	The planned sample size is approximately 130 patients (65 patients in each treatment arm). This sample size will yield >85% power to detect a treatment difference of 24% in the proportion of patients achieving IGA hand and foot (0, 1) at week 16 between placebo (10%) and dupilumab (34%) at a 2-sided significant level of 5% using Chi-square test and assuming a dropout rate of 10%. The assumed treatment difference of 24% is based on the effect of 26% observed in dupilumab phase 3 monotherapy studies in adult patients with AD, and adjusted to account for the potential inclusion of some patients with ACD who would be missed with certain patch testing (ie,, TRUE test) at screening. It is reasonable to assume that the effect size of dupilumab on AD of hands and feet would be similar to that seen in in previously conducted phase 3 trials in generalized AD, as the underlying pathophysiology is the same. Moreover, a recent observational study to compare the effect of dupilumab on hand lesions vs. lesions on other parts of the body found a high degree of concordance in terms of onset of effect and overall effect at week 16. **Efficacy Analysis Sets** The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated at randomization (as randomized). The per protocol set (PPS) includes all patients in the FAS except for those who are excluded because of specified important protocol deviations.

All efficacy variables will be evaluated on the FAS; the primary endpoint will also be evaluated on the PPS. Analysis on the FAS will be considered to be primary.

Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

Pharmacokinetic Analysis Sets

The PK analysis population includes all patients/subjects who received any study drug and who had a at least 1 non-missing result following the first dose of study drug.

Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received any study drug and had at least 1 non-missing ADA result following the first study dose.

The neutralizing antibody (NAb) analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA negative are set to negative in the NAb analysis set).

Analysis Methods:

Primary Efficacy Analyses

The primary endpoint of proportion of patients achieving an IGA score of 0 or 1 on hand and foot at week 16 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test to assess the difference in the proportion of responders in the FAS adjusting for the randomization stratification factors (age [adults vs. adolescents], disease severity of IGA hand and foot [3 vs. 4], and geographic region [United States versus Japan versus other countries]).

To account for use of rescue treatment, patients will be considered as non-responders for all time points subsequent to the use of rescue treatment in the primary analysis. If a patient has missing value with any reason for IGA on hand and foot assessment at week 16, the patient will be classified as a non-responder at week 16.

Sensitivity analysis using the last observation carried forward (LOCF) approach or the worst observation carried forward (WOCF) approach to determine patient's status at week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. The efficacy data will be set to missing after rescue treatment is used, then the LOCF or WOCF method will be used to determine patients' status at week 16.

In addition, the CMH method adjusted by randomization strata will also be performed on all observed data regardless if rescue treatment is used. A patient with missing data will be counted as a non-responder. Other sensitivity analyses may be conducted.

Subgroup analysis (eg, by age group, by anatomical area of involvement [hand involvement only vs. involvement of hand and foot or foot involvement only]) will also be performed.

Secondary Efficacy Analyses

Secondary efficacy endpoints that measure binary responses (eg, improvement of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16) will be analyzed in the same fashion as the primary analysis.

Continuous secondary efficacy endpoints (eg, percent change mTLSS for hand/foot lesions from baseline to week 16) will be analyzed using an analysis of covariance (ANCOVA) model for the FAS with treatment group, randomization stratification factors (age [adults vs. adolescents], disease severity of IGA hand and foot [3 vs. 4], and geographic region [United States versus Japan versus other countries]), and relevant baseline measurement included in the model. Similarly, to account for the impact of rescue treatment on the efficacy effect, patients' efficacy data through week 16 after the rescue treatment use will be set to missing. The missing data for continuous endpoints will be imputed by the pattern-mixture approach where the WOCF approach will be used for the missing due to rescue treatment, AE, and lack of efficacy and the multiple imputation (MI) approach will be used for the missing due to other reasons. The MI Statistical Analysis Software (SAS) procedure with Markov Monte Carlo algorithm will be applied in the MI for multiple times. The complete datasets created based on the pattern-mixture approach will be analyzed using the ANCOVA model defined previously, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula.

All efficacy data will be used for analysis regardless of whether the patient is on study treatment or discontinues the study treatment but remains in the study. In addition, the MI with the ANCOVA model and the ANCOVA model based on LOCF or WOCF imputation method will be performed as sensitivity analyses. Other sensitivity analysis such as the MI approach with ANCOVA model on all observed data regardless of rescue treatment use will also be conducted. Additional details on sensitivity analyses will be provided in the SAP.

Control of Multiplicity

	Type I error rate will be controlled using a hierarchical testing procedure for the primary and secondary efficacy endpoints at the 2-sided 0.05 level. The hierarchy order will be specified in the SAP prior to database lock. Safety Analysis Safety analysis will be based on the SAF. This includes reported TEAEs, AESIs, and other safety information (eg, clinical laboratory evaluations, vital signs). A summary of safety results for each treatment group will be presented.

1. INTRODUCTION

Hand and foot dermatitis is an umbrella term that includes irritant contact dermatitis (ICD), allergic contact dermatitis (ACD) and patients with a history of, or presence of concurrent atopic dermatitis (AD), which is also known as atopic hand and foot dermatitis (Agner, 2015). The morphological types that have been described in this condition include the following: vesicular (dyshidrotic), hyperkeratotic, fissured, and nummular (Menne, 2011).

Patients with AD are at increased risk of hand dermatitis of any etiology as compared to the general population with a 3 to 4-fold increase of prevalence as compared to controls (Ruff, 2018). The prevalence of hand dermatitis in patients with AD has been reported to be approximately 60% (Simpson, 2006). Similarly, the prevalence of foot dermatitis in patients with AD has been reported to be approximately 30% (Holm, 2016). Atopic dermatitis is a known risk factor for development of hand dermatitis with approximately 28% of patients with hand dermatitis having a history of AD (Petersen, 2014). Similarly, a history of AD is present in approximately 14% of patients with foot dermatitis (Agner, 2015). Atopic conditions apart from AD, such as allergic rhinitis and asthma, have also been associated with atopic hand and foot dermatitis (Scalone, 2015).

Atopic hands and feet dermatitis (also known as atopic hand and foot eczema)[1] presents with redness, infiltration, scaling, vesicles, areas of hyperkeratosis, and cracks (fissures) (Coenraads 2012). Lesions are associated with significant itching and pain. The morphology tends to evolve over time and many patients can have a mixed presentation. In the majority of patients, the same morphological subtype is found on the hands and feet (Brans, 2015).

The disease tends to be chronic and recalcitrant with a substantial impact on quality of life (QoL), comparable with other skin diseases like psoriasis (Agner, 2008). Chronic hand dermatitis has also been associated with significant detrimental effect on work productivity, activity impairment, and heath care costs (Fowler, 2006). It has been shown that 65% of patients with severe hand dermatitis reported loss of productivity at work, with an average of 10.1 days per patient per month (Politiek, 2016). Moreover, in certain occupations like hairdressers, bakers, and machine workers, up to 18% of patients had to change jobs due to hand dermatitis (Meding, 2005).

Atopic hand and foot dermatitis has the same underlying pathophysiology as in other parts of the body and is caused by a complex interaction of genetics, defects in skin barrier function, environmental exposure to irritants, and immunologic responses. In addition, it has been suggested that abnormal cholinergic responses in the form of palmar and plantar hyperhidrosis specifically contribute to the development of H-F dermatitis of AD (Lee, 2001) Type 2 helper T cell (Th2) mediated immune response is believed to play a central role in the pathogenesis of AD, including that of hands and feet. The skin lesions of AD are characterized by increased expression of proinflammation type 2 cytokines, such as interleukin (IL)-4 and IL-13, and by skin infiltration of Th2 and other inflammatory cells. The elevated immunoglobulin E (IgE) responses and eosinophilia observed in the majority of patients with AD reflects an increased expression of the type 2 cytokines IL-4 and IL-13 (Leung, 1999)

[1] For the purpose of this protocol, atopic hands and feet dermatitis refers to involvement of either hands only, feet only, or both hands and feet.

The other 2 major causes for hand and foot dermatitis, apart from AD, are ICD and ACD. It should be noted that the morphological presentation of all these etiologies can be very similar, and it is hard to delineate the etiology just based on clinical examination. Recently there has been a trend to obtain further disease classification in hand and foot dermatitis to focus on etiology rather than morphology as this approach offers the advantage of targeting prevention and, in some cases, also providing more specific treatment (Johansen, 2011). These 2 forms of dermatitis are unlike AD; these forms are not primarily driven by type 2 immune responses (Gittler, 2013).

The management of AD of hand and foot is based upon prevention and avoidance strategies using gloves, reducing exposure to irritants and regular use of emollients. Step therapy is used with an approach to initiate treatment with topicals and then progress to systemics in case of inadequate response to topicals (Diepgen, 2007). Short courses of topical corticosteroids (TCS) are recommended as first line treatment to control flares. Long term application of TCS comes with risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, growth retardation, hypothalamic-pituitary axis effects, etc). Treatment guidelines for hand dermatitis of any etiology recommend continuous long-term treatment beyond 6 weeks be performed only when necessary and under careful medical supervision (Diepgen, 2007). Topical calcineurin inhibitors may be considered for patients with AD of hand and foot who require long-term need for treatment, although evidence for their efficacy is limited. The low penetration/permeation of topical agents through the skin of the hands and feet explains the limited efficacy of topical anti-inflammatory agents. Overnight occlusion may be advocated to allow for sufficient penetration of topical anti-inflammatory drugs. However, in the long-term, such measures are frequently unpractical and cumbersome for patients.

There is no Food and Drug Administration (FDA) approved systemic therapy for localized atopic hand and foot dermatitis. Alitretinoin (oral retinoid) is the only approved systemic therapy in the European Union (EU), for severe chronic hand dermatitis (including AD of hands) but has significant side effects (Ruzicka, 2008). Most common adverse events (AEs) seen in phase 3 trials were headache, dry skin, conjunctivitis, hypercholesterolemia, and flushing. Significant known side effects are psychiatric effects such as depression, mood changes and suicidal ideation, changes in bone mineralization, and benign intracranial hypertension. Alitretinoin also requires strict contraception measures in women of childbearing potential due to high teratogenic potential. Although systemic corticosteroids can be effective symptomatic treatment in acute hand eczema or acute flares of chronic hand eczema, chronic use is not recommended due to potentially serious long-term side effects. Systemic immunomodulators such as cyclosporine, azathioprine and methotrexate have very little evidence from randomized controlled trials to support their use in AD of hand and foot and are associated with significant side effects.

Dupilumab (brand name DUPIXENT®) is approved in over 40 countries worldwide including the United States (US), EU, and Japan for the treatment of moderate-to-severe AD in adults. Dupilumab was also authorized in the US and EU recently for use in adolescent patients (≥12 years) with inadequately controlled moderate-to-severe AD. Dupilumab is a novel targeted immunoregulatory agent that selectively and simultaneously inhibits IL-4 and IL-13 signaling by blocking the obligate shared component of the IL-4/IL-13 receptor complex. It is intended to inhibit key disease drivers to achieve clinical benefit without the side effects commonly observed with existing non-selective systemic immunosuppressants. Additional background information on the study drug and development program can be found in the Investigator's Brochure.

It is known that severe atopic hand and foot dermatitis can be particularly difficult to treat. Although dupilumab is efficacious in AD more broadly, its effect specifically in treating localized atopic hand and foot dermatitis has not been studied. Several case reports have recently demonstrated efficacy of dupilumab in atopic hand and foot dermatitis (Zirwas, 2018). This is not surprising given the lesions of AD share the same underlying type 2 driven pathophysiology, irrespective of body location. However, atopic hand and foot dermatitis can be difficult to distinguish clinically from allergic or irritant eczema. This study, by generating data on the effect of dupilumab on AD lesions of the hand and feet and providing an algorithm to identify patients who are candidates for dupilumab therapy, is intended to facilitate access to a promising new therapy for patients with a recalcitrant and debilitating form of AD.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the efficacy of dupilumab on skin lesions in patients with atopic hand and foot dermatitis.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the efficacy of dupilumab on various other domains (pruritus, pain, sleep loss, health related QoL, work life impairment) in patients with atopic hand and foot dermatitis
- To evaluate the safety and tolerability of dupilumab administered to patients with atopic hand and foot dermatitis
- To evaluate systemic exposure and immunogenicity of dupilumab in patients with atopic hand and foot dermatitis

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To study dupilumab's mechanism of action (related to efficacy and/or safety), why some patients respond better than others (safety and/or efficacy), IL4R pathway, atopic hand and foot dermatitis and related diseases
- To assess the concordance between treatment effect of dupilumab on a) atopic hand and foot dermatitis lesions and b) concomitant AD lesions on other parts of the body
- To evaluate exposure-response relationships

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Signs and symptoms of AD of hands and feet, like other parts of the body, are driven by type 2 inflammation. Dupilumab monotherapy, by blocking type 2 inflammation, will result in an improvement in various domains of disease in adult and adolescent patients with moderate-to-severe atopic hand and foot dermatitis inadequately responsive to topical corticosteroids. This includes effect on various measures of intensity and extent of skin lesions on hand and foot, symptoms such as pruritus, sleep loss and pain, QoL, work life impairment, and mental health.

3.2. Rationale

3.2.1. Rationale for Study Design

Dupilumab is the first globally approved therapy for moderate-to severe AD. Its efficacy, both as monotherapy and in conjunction with corticosteroids, has been demonstrated in multiple double-blind, randomized, clinical trials (Simpson, 2016) (Thaci, 2016). In all the reported trials inclusion criteria mandated that AD must affect greater than 10% of the Body Surface Area (BSA). Because the palm including the fingers comprises 1% of the BSA, the studies specifically excluded patients with AD limited to the hands. Similarly, the feet represent a small BSA much lower than 10%. These trials evaluated the global effect of dupilumab on AD lesions on the whole body without discrimination by body regions such as hands and feet. Similarly, these trials did not evaluate the effect of dupilumab on symptoms such as pruritus and pain resulting specifically from hand and foot disease. A dedicated clinical study using investigator assessments and patient reported outcomes focused on disease in hand and feet is needed to evaluate such effects.

Atopic hand and foot dermatitis can be significantly debilitating and can cause unique problems such as reduced work productivity, prolonged sick leave and ultimately job loss (Fowler, 2006). The impact on QoL of hand dermatitis has been found to be comparable to that with moderate-to-severe AD (generalized) and psoriasis (Agner, 2008). This study, by generating data on the effect of dupilumab on AD lesions of the hand and feet, is intended to facilitate access to a promising new therapy for patients with a recalcitrant and debilitating form of AD.

Hand and foot dermatitis has multiple underlying etiologies with AD, ACD, and ICD recognized as the major causes. The pathophysiology of hand and foot dermatitis varies depending upon the underlying etiology (Gittler, 2013). Atopic hand and foot dermatitis is believed to be classically type 2 inflammation-mediated. Allergic contact dermatitis is classically believed to be Th1 mediated disorder. Irritant contact dermatitis is primarily caused due to damage to skin barrier and is believed to be mediated by innate immunity (IL-1, TNFα).

Several case reports have recently demonstrated efficacy of dupilumab in AD of hand and foot (Nanda, 2019) (Oosterhaven, 2018) (Zirwas, 2018). These patients had previously failed treatment with various topical and systemic therapies used in hand and foot dermatitis. In the case series published by Zirwas et al, all 3 patients met the diagnostic criteria for AD and had total BSA<10%. All 3 patients underwent comprehensive patch testing and no relevant allergens were detected. In contrast to these case reports, dupilumab has been shown to have a variable effect on ACD, with many patients reporting no improvement with use of dupilumab (Stout, 2019). Moreover, there

have been case reports of patients with AD in whom failure of resolution of lesions in certain parts of the body was caused due to concomitant presence of ACD (Suresh, 2018).

Given the unclear scientific rationale for dupilumab in forms of hand and foot dermatitis other than atopic hand and foot dermatitis, as well as the variable results reported in the literature of the effect of dupilumab on ACD, the patient population in this study will exclude patients with these other dermatides.

Limiting the study population with moderate-to-severe forms of disease (Investigator Global Assessment [IGA] hands and feet of 3 or 4), chronic disease (disease present for at least 6 months prior to screening visit) and with disease inadequately responsive to TCS or in patients in whom TCS are inadvisable, will ensure that the patients with highest unmet medical need will be enrolled in this study. Moreover, should the study demonstrate adequate safety and efficacy, the approach used in this study can be applied in clinical practice as an algorithm to identify patients for dupilumab therapy.

A blinded, randomized, placebo-controlled design is chosen to minimize bias in data collection and result interpretation. The presence of a placebo arm is appropriate for the objectives of this study as this will allow for the most robust assessment of the efficacy and safety of dupilumab.

A monotherapy design has been chosen to allow a true estimate of the effect size of dupilumab without any confounding by use of topical or systemic therapies. This is especially pertinent to hand and foot dermatitis as due to thicker skin of palms and soles, higher potency TCS or TCS under occlusion might be needed which have potential to confound study results. Patients will be allowed to be rescued with topical/systemic therapies in case of intolerable symptoms.

The primary endpoint used in the study is based on the endpoint used in previous phase 3 dupilumab AD trials (IGA), which is adapted to assess hand and feet involvement only. A similar instrument was used in the phase 3 trial for alitretinoin for hand dermatitis. Moreover, there is precedence of adapting the IGA to measure outcomes in localized forms of disease for scalp and nail psoriasis in phase 3 trials for biologics (secukinumab for scalp psoriasis and adalimumab for nail psoriasis) (Bagel, 2017) (Elewski, 2018).

The 16-week treatment duration is similar to that used in previous adult phase 3 trials in AD. Moreover, the selected dupilumab dose regimens will have achieved steady-state concentration by the end of this period. A recent observational study to compare effect of dupilumab on hand lesions vs. lesions on other parts of the body found a high degree of concordance in terms of onset of effect and overall effect at week 16 (Oosterhaven, 2018). The only drug approved for hand dermatitis, alitretinoin, is a slow acting drug showing modest efficacy after 24 weeks. The response of hand dermatitis to systemic immunomodulatory agents used in AD is rapid. As an example, oral cyclosporine has shown efficacy in hand dermatitis in a 6-week randomized controlled trial (Granlund, 1996).

The 12-week follow-up period is based on the expected pharmacokinetics (PK) of dupilumab after the last dose, ie, the time for serum concentrations to decline to nondetectable levels (below the lower limit of quantification) in most patients.

Randomization will be stratified to control for potential confounding variables which could impact efficacy (age [adults vs. adolescents], disease severity [IGA hand and foot 3 vs. 4], and geographic region [United States versus Japan versus other countries]).

3.2.2. Rationale for Dose Selection

The dose regimen of dupilumab selected for this study is an initial (loading) dose of 600 mg administered subcutaneously (SC), followed by 300 mg administered SC every 2 weeks (Q2W) in adults and a fixed dose tiered by body weight in adolescent patients (body weight ≥60 kg, an initial [loading] dose of 600 mg administered SC, followed by 300 mg administered SC Q2W; body weight <60 kg, an initial [loading] dose of 400 mg administered SC, followed by 200 mg administered SC Q2W). The respective dose regimens have proven to be effective and have demonstrated an acceptable safety profile in adult and adolescent patients with moderate-to-severe AD. Given the substantial evidence gathered regarding dose selection with dupilumab in AD and considering that pathophysiology of AD elsewhere is identical to that of atopic hand and foot dermatitis, the dose of dupilumab approved in the US, EU, and other countries globally for use in AD will be tested in this study. This is especially relevant as atopic hand and foot dermatitis tends to co-exist with AD on other parts of the body in majority of the patients (Agner, 2015).

The case reports published in the literature that showed substantial benefit for dupilumab in patients with AD of hands and feet used the approved dupilumab dosing regimen, thus provide further support for this dosing regimen (Nanda, 2019) (Oosterhaven, 2018) (Zirwas, 2018). The observational study cited in the previous section, which showed a high degree of concordance between effect on lesions of atopic hand dermatitis vs. lesions on other parts of the body, also used the approved dupilumab dosing regimen providing further credence to this approach (Oosterhaven, 2018).

The administration of the loading dose of dupilumab will allow systemic concentrations to reach steady-state faster, and potentially reduce the time to onset of clinical effect.

3.3. Risk-Benefit

Benefits

The efficacy of dupilumab in AD was evaluated in multiple randomized, double-blind, placebo-controlled studies in adults and in a separate study with a similar study design in adolescents. In all studies, dupilumab demonstrated clinically meaningful and statistically significant improvements compared to placebo in disease activity measures assessing objective AD signs (IGA, Eczema Area and Severity Index [EASI], SCORing AD [SCORAD], BSA affected by AD), subjective symptoms (eg, Pruritus Numeric Rating Scale [NRS], Patient Oriented Eczema Measure [POEM]), and quality of life (Dermatology Life Quality Index [DLQI] in adults, Childrens' Dermatology Life Quality Index [CDLQI] in adolescents). These results formed the basis for approval of dupilumab for moderate-to-severe AD in adults worldwide, and in adolescents in US and EU.

Although the above trials did not specifically look at the effect of dupilumab on hand and foot dermatitis, post hoc analyses from phase 3 trials showed that dupilumab works equally well across different anatomical regions (upper limbs/lower limbs/trunk/head and neck) (Blauvelt, 2017). In the post approval setting, multiple case reports have shown that patients with atopic hand and foot dermatitis receive substantial clinical benefit from treatment with dupilumab (Nanda, 2019) (Oosterhaven, 2018) (Zirwas, 2018)This is consistent with the known pathophysiology of AD which is driven primarily by type 2 inflammation, irrespective of the site of location.

Risks

The most common adverse drug reactions identified in the dupilumab adult AD clinical program were injection site reactions common (≥10%). Other common adverse reactions (≥1% and <10%) included conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, eye pruritus, dry eye, blepharitis, oral herpes, herpes simplex (primarily mucocutaneous in nature) and eosinophilia. In the completed adolescent AD studies, the safety profile was consistent with that reported in adults and there were no new safety signals detected with dupilumab in the adolescent population.

Overall, systemic hypersensitivity has been established an important identified risk with dupilumab. As protein therapeutics, all monoclonal antibodies (mAbs) are potentially immunogenic. Rare serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD and anaphylaxis related to dupilumab in the adult asthma clinical trials. No event of serum sickness/serum sickness-like reaction or anaphylaxis related to dupilumab has been reported in the adolescent AD program.

In study R668-AD-1924, patients will be monitored at the study center for 30 minutes post-dose for the first 3 visits at which study drug is administered to facilitate detection and treatment of any immediate hypersensitivity reactions to the study drug.

An important potential risk "Eosinophilia associated with clinical symptoms" has been observed in the asthma clinical trials (few cases of eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia) but not in AD clinical studies.

Risk/Benefit Conclusion

The safety data available to date, in conjunction with the risk monitoring and mitigation strategies in the study protocol, and the clinical benefit of dupilumab demonstrated in multiple AD studies in adult and adolescent patients, support a favorable benefit-risk profile for dupilumab.

A risk-benefit statement with respect to the overall development program is provided in the Investigator's Brochure.

Study Conduct in Response to COVID-19

Recognizing that "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patient in this study until the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in the study. Until then, the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

- Proportion of patients achieving an IGA (hand and foot) score of 0 or 1 at week 16

4.1.2. Secondary Endpoints

Key Secondary Endpoint for Efficacy:

- Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥4 from baseline to week 16

Secondary Endpoints for Efficacy:

- Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥3 from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily hand and foot peak Pruritus NRS
- Percent change in mTLSS for hand/foot lesions from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily hand and foot peak Pain NRS
- Percent change from baseline to week 16 in weekly average of daily Sleep NRS
- Change from baseline to week 16 in percent surface area of hand and foot involvement with AD
- Percent change from baseline to week 4 in weekly average of daily hand and foot peak Pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥4 from baseline to week 4
- For patients with hand dermatitis, percent change from baseline to week 16 in Hand Eczema Severity Index (HECSI) score
- For patients with hand dermatitis, proportion of patients with HECSI-75 at week 16
- For patients with hand dermatitis, proportion of patients with HECSI-50 at week 16
- For patients with hand dermatitis, proportion of patients with HECSI-90 at week 16
- For patients with hand dermatitis, change from baseline to week 16 in Quality of Life in Hand Eczema Questionnaire (QOLHEQ)
- Change from baseline to week 16 in Work Productivity and Impairment (WPAI) and Classroom Impairment Questionnaire (CIQ)

Secondary Endpoint for Safety:

- Incidence of treatment-emergent adverse events (TEAEs) through week 16

Secondary Endpoints for Clinical Pharmacology and Immunogenicity:

- Trough concentration of functional dupilumab in serum at various time points
- Incidence of treatment-emergent anti-drug antibody (ADA) and titer over time

4.1.3. Other Endpoints and Assessments

Other endpoints and assessments, as applicable, will be specified in the Statistical Analysis Plan (SAP).

4.1.4. Exploratory Endpoints

- In patients with AD lesions on other parts of the body in addition to hands and feet;
  - Percent change in EASI score from baseline to week 16
  - Proportion of patients with IGA score of 0/1 at week 16
  - Proportion of patients with EASI-75 at week 16

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics including medical history, and medication history for each patient.

5.2. Efficacy Variables

The efficacy variables include measurements or scores for individual patients for the following:

- Patient-reported outcome measures: Daily hand and foot peak Pruritus NRS, Daily hand and foot peak Pain NRS, Daily Sleep NRS, QOLHEQ, Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), WPAI+CIQ, and EQ-5D
- Investigator-reported outcomes: IGA for hands and feet, mTLSS, percent surface area of hand and foot involvement with AD, HECSI, IGA (global), and EASI

5.3. Safety Variables

The safety variables include recordings, measurements or laboratory test results for individual patients for the following: AEs, vital signs, physical examinations, hematology, blood chemistry, and urinalysis.

5.4. Pharmacokinetic Variables

The PK variable is the concentration of dupilumab at each time point. These sampling timepoints are specified in Table 1 .

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1 .

5.6. Pharmacodynamic and Other Biomarker Variables

Not applicable.

6. STUDY DESIGN

This is a global, multicenter, randomized, double-blind, parallel-group, placebo-controlled study investigating the efficacy and safety of dupilumab monotherapy in adult and adolescent patients with moderate-to-severe atopic hand and foot dermatitis. Eligible patients must have a documented history of inadequate response or intolerance to treatment of hand and foot dermatitis with topical AD medications. Approximately 130 patients will be enrolled for the study. The number of adult patients will be capped at approximately 100 to ensure that, at a minimum, approximately 30 adolescents will be enrolled. The number of patients with hands only involvement will be capped at approximately 100.

6.1. Study Description and Duration

The study consists of 3 periods:

- Screening period (minimum duration of 4 weeks and maximum up to 8 weeks)
- Randomized treatment period (16 weeks)
- Post treatment follow-up period (12 weeks)

At the screening visit, adult patients will provide informed consent before any other study procedures are conducted. For adolescent patients, parents or legal guardians will provide informed consent and the patients will provide assent. After providing informed consent/assent, the patients will be assessed for study eligibility at the screening visit. During the screening period, systemic treatments for AD will be washed out, as applicable, according to the eligibility requirements. Topical treatments for AD of hands and feet will also be discontinued, according to the eligibility requirements. However, patients will be allowed to use topical treatments for treatment of AD on other parts of the body with certain restrictions (Section 8.10.2).

A detailed history of exposure to irritants relevant to hand and foot dermatitis in the occupational as well as non-occupational setting will be elicited at screening. During the screening period, patients will be provided instructions on skin protection measures. Patients will need to follow these measures throughout the screening period in order to remain eligible for the study. It is recommended that patients continue with these measures during the remaining duration of the study (for details of skin protection measures refer to Section 8.10.3).

Patients may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions (eg, inability to conduct patch testing during the screening period, medication use, intercurrent illness, transient medical condition), unless the reason for the screen failure is related to failing the disease severity inclusion criteria.

Patch testing with a standard series of allergens will also be carried out during the screening period to exclude patients with predominantly ACD of hand and foot. Patients will need to be discontinued from topical/systemic medications for AD prior to the patch testing. Patients will be called to the site for multiple visits during the screening period for conducting these patch tests (refer to Section 9.2.1.1 for further details on the patch testing procedure).

Patients who meet the eligibility criteria will be randomized (1:1) to one of the following treatment groups:

- Dupilumab, administered SC Q2W
  - in adults; dupilumab 300 mg, after a loading dose of 600 mg on day 1, irrespective of body weight
  - in adolescents; Body weight ≥60 kg, dupilumab 300 mg, after a loading dose of 600 mg on day 1, body weight <60 kg, dupilumab 200 mg, after a loading dose of 400 mg on day 1.
- Matching placebo with the above respective dupilumab doses, administered SC Q2W

Randomization will be stratified by age (adults vs. adolescents), disease severity (IGA hand and foot 3 vs. 4), and geographic region (United States versus Japan versus other countries). Randomization will be capped for the adults at approximately 100 to ensure that, at a minimum, approximately 30 adolescents will be enrolled.

Information on the anatomical area of involvement (hands only vs. hands and feet vs. feet only) will be collected at baseline prior to randomization. The number of patients with hands only involvement will be capped at approximately 100.

During the treatment period, patients will have in-clinic visits at week2 and week4, and then in-clinic visits every 4 weeks through week 16 with bi-weekly phone visits in between the in-clinic visits. Patients and/or parents/caregivers (in case of adolescents as deemed appropriate based on age of patient) will be trained on injecting study drug during in-clinic visits when study drug is administered (day 1, week 2, and week 4). During weeks in which no in-clinic visit is scheduled, patients will either self-inject study drug or the parent/caregiver will administer study drug to the patient. In case patients do not want to self-inject and the parent/caregiver do not want to administer study drug to patient, patients may have the clinic staff administer all the study drug injections in the clinic. Safety laboratory tests, collection of samples for study drug concentrations, immunogenicity, and clinical assessments will be performed at specified clinic visits, as noted in Table 1.

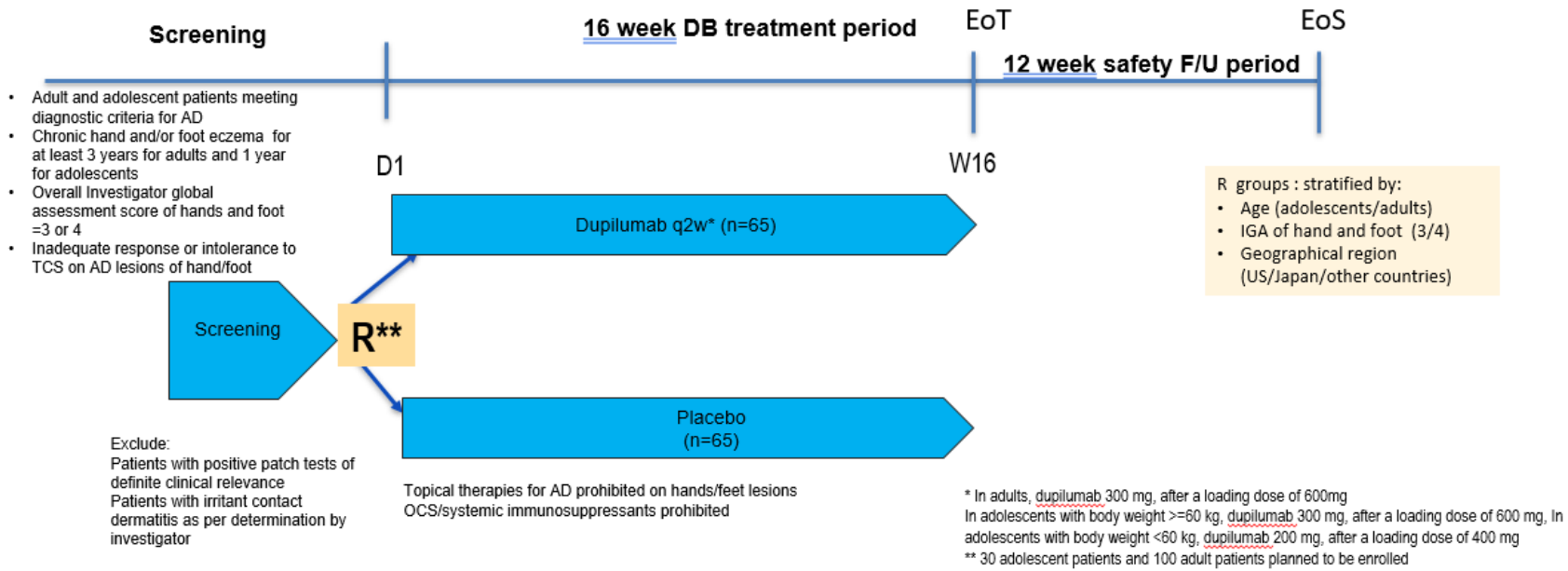
The use of topical and systemic medications for the treatment of atopic chronic hand and foot dermatitis will be prohibited during the treatment period. However, patients will be allowed to use topical medications for AD on parts of the body other than hand and foot. These topical medications will be limited to low to medium potency TCS creams. Moreover, patients will be advised to either a) use gloves or use tongue depressors while applying these creams if self-applying or b) have a caregiver apply these treatments. If medically necessary (ie, to control disease flares), rescue treatment in the form of high potency TCS on hand/foot and/or systemic immunosuppressants may be provided to study patients at the discretion of the investigator. Patients may continue study treatment if they received rescue treatment.

The end of treatment visit will occur at week 16, 2 weeks after the last dose of study drug. The primary endpoint will be assessed at this visit. If patients prematurely discontinue study drug, the patients will be encouraged to stay in the study to have data collected at all remaining scheduled visits until completion of the planned end of study visit.

Post-treatment follow-up period: Upon completing the 16-week randomized treatment period, patients will enter a 12-week follow-up period. The end of study (EOS) visit will occur at week 28.

An overview of the study is provided in the study schematic below (Figure 1).

Figure 1: Study Flow Diagram



D=Day; DB=Double-blind; EOS=End of study; EOT=End of treatment; F/U=Follow-up; OCS=oral corticosteroid; R=Randomization; W=Week.

6.1.1. End of Study Definition

The end of study is defined as the date of the last visit of the last patient in the study.

6.2. Planned Interim Analysis

No interim analysis with alpha spending is planned for this study.

Timing of data analyses are described in Section 11.5.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 130 patients (65 patients per arm) will be enrolled at approximately 50 global sites. The number of adult patients will be capped at approximately 100 to ensure that, at a minimum, approximately 30 adolescents will be enrolled. The number of patients with hands only involvement will be capped at approximately 100.

7.2. Study Population

The proposed study population is patients with chronic, moderate-to-severe atopic hand and foot dermatitis inadequately responsive to medium-to-high-potency TCS or in whom medium-to-high-potency TCS are inadvisable. Only patients meeting the diagnostic criteria for AD will be included in this study. Patients with a confirmed diagnosis of irritant contact dermatitis or ACD as the predominant cause of hand and foot dermatitis will be excluded from the study.

7.2.1. Inclusion Criteria

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

1. Male or female ≥12 years old at time of the screening visit.
2. Patients with chronic hand and foot dermatitis diagnosed at least 3 years prior to the screening visit for patients ≥18 years old, and at least 1 year prior to the screening visit for patients ≥12 to <18 years old.
3. Patients with involvement of at least 2 anatomical areas at screening and baseline. These 2 anatomical areas could be both hands, 1 hand and 1 foot, or both feet.
4. Patients need to have an IGA hand and foot score of 3 or 4 (moderate-to-severe disease) at screening and baseline.

   Note: The investigators should assign a single IGA score based on their overall impression of disease severity of hands and feet. Patients need to have overall moderate-to-severe disease in hands/feet and involvement of at least 2 anatomical areas to be eligible.
5. Patients with documented recent history (within 6 months before the screening visit) of inadequate response of atopic hand and foot dermatitis to topical medication(s) or for

whom topical treatments of atopic hand and foot dermatitis is medically inadvisable (eg, intolerance, because of important side effects or safety risks). If documentation is inadequate, potential patients may be offered a course of treatment with a daily regimen of TCS of medium or higher potency (±TCI as appropriate), applied for at least 28 days during the screening period, or for the maximum duration recommended by the product prescribing information, whichever is shorter. Patients who demonstrate inadequate response during this period, as defined above, will be eligible for inclusion in the study following appropriate washout.

NOTES:

- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state as per clinical judgment of treating physician despite treatment with a daily regimen of TCS of medium to higher potency (± topical calcineurin inhibitor [TCI] as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever is shorter.
- Important side effects or safety risks from treatment of atopic hand and foot dermatitis are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy of hand and feet, and systemic effects, as assessed by the investigator or by the patient's treating physician.
- Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician.
- Patients with documented systemic treatment (systemic immunosuppressant drugs like cyclosporine, methotrexate, corticosteroids, alitretinoin, etc) for atopic hand and foot dermatitis in the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with dupilumab after appropriate washout. However, this does not apply to patients who used these systemic treatments for generalized AD lesions throughout the body. Moreover, this also does not apply to cases in which a determination cannot be made with reasonable certainty that the systemic treatment was used in the past specifically for atopic hand and foot dermatitis.

6. Patients need to meet the Hanifin and Rajka criteria for diagnosis (Hanifin, 1980).

   NOTES:

   The diagnosis of AD requires the presence of at least 3 of 4 major criteria:

   a. Pruritus
   b. Dermatitis affecting flexural surfaces in adults and the face and extensors in infants (criterion: criterion quoted verbatim, infants will not be included in this study)
   c. Chronic or relapsing dermatitis
   d. Personal or family history of cutaneous or respiratory atopy
      In patients who do not have AD lesions present on parts of the body other than hands and feet at time of screening, the study investigator should check for any prior history of presence of AD lesions in typical age specific distribution patterns for eg, flexural

areas (cutaneous atopy). Prior history of respiratory atopic diseases (for eg, asthma, allergic rhinitis) should also be elicited.

In addition, 3 out of 23 minor criteria need to be met (refer to Appendix 1 for a list of the minor criteria).

7. Baseline hand and foot peak Pruritus NRS score for maximum itch intensity ≥4.
8. At least 11 (of a total of 14*) applications of a topical emollient (moisturizer) during the 7 consecutive days immediately before the baseline visit (not including the day of randomization).

   * Based on application of moisturizer twice daily for 7 days leading up to randomization. Application of emollient more than twice in a day is permitted but the additional applications will not be counted in the 11 required applications to fulfil eligibility for the study.
9. Willing and able to comply with clinic visits and study-related procedures.
10. Provide informed consent/assent signed by study patient or legally acceptable representative.
11. Able to understand and complete study-related questionnaires.
12. Patients need to have been compliant with the skin protection measures (as outlined in Section 8.10.3) through the entire duration of the screening period (minimum of 4 weeks but lasting to a maximum of 8 weeks). This includes avoidance of known irritants that are identified as causing exacerbation of one's hand and foot AD.

7.2.2. Exclusion Criteria

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

1. Patients with a positive patch test reaction to one or more allergens (a score of 1+ or above according to International Contact Dermatitis Research Group [ICDRG] grading scale) in either

   a. the baseline patch test series OR
   b. extended baseline or supplemental patch test allergens if such additional testing is conducted by the investigator OR
   c. Personal products if testing with such products is conducted by the investigator

   AND

   Which is deemed to be clinically relevant in the view of the investigator as the current cause of the hand and foot dermatitis.

   NOTES:

   - Patch testing with extended baseline series, supplemental series and/or personal products will only be carried out if deemed necessary as per clinical judgment of investigator

- The results of the patch tests conducted in the past can be used to determine eligibility for a patient as long as ALL of the following are met:
  - the patch testing was conducted no more than 3 years prior to screening visit AND
  - patch testing was conducted with the same battery of allergens as the baseline Patch test series or even if conducted with a different series included all the allergens included in the baseline patch test series AND
  - the investigator does not deem patch testing with an extended baseline series, supplemental series or with patient's personal products necessary based on clinical judgment.
- Patients with a documented diagnosis of ACD of hands and/or feet, who have a positive patch test reaction at screening will also be excluded from the study, regardless of whether history of current skin exposure to products containing this allergen (current relevance) is present.
- Patients with positive reactions which are interpreted as irritant reactions based upon morphology, timing (eg, 1 +ve at day 2 followed by a decrescendo pattern) will still be eligible for study as long as they meet other eligibility criteria for the study.

2. Patients with a documented diagnosis of protein contact dermatitis of hands and/or feet. These are patients with occupational or non-occupational contact to proteins such as food, latex etc. with positive prick test who present with lesions of contact urticaria or dermatitis on hands/feet.
3. Patients in whom patch testing cannot be conducted due to any reason (these include but are not limited to refusal of patient to have patch testing, inability to take patient off systemic immunosuppressants/topical AD medications for the required washout period prior to patch testing, lack of clear skin (free of lesions) on upper back and /or upper arm on which to apply patch tests, etc).
4. Patients with documented exposure to irritants in the occupational or non-occupational (household/recreational) setting that is believed to be a predominant cause of the current hand and foot dermatitis as per the judgment of the investigator. A detailed history of exposure to irritants in the occupational as well as non-occupational setting will be elicited at screening. The site staff will complete a CRF containing a list of irritants commonly implicated in causing irritant contact dermatitis at screening.

NOTES:

- It is recognized that patients with atopic hand and foot dermatitis may have identified irritants which are known to exacerbate their disease. As long as the irritants are a) neither the primary nor the predominant cause for their disease as per clinical judgment of investigator and b) the patients are willing to avoid these irritants during the entire duration of the study, such patients can be enrolled into the study.
- Patients whose hand dermatitis, in the clinical judgment of investigator, is predominantly irritant contact dermatitis caused due to household or occupational wet work exposure will also be excluded. As a guide, investigators can use the following

wet work criteria; (a) activities where workers have to immerse their hands in liquids for >2 hours per shift, b) wear waterproof (occlusive) gloves for a corresponding amount of time, or c) wash their hands >20 times per shift (Behroozy et al. 2014) to make this determination.

5. Treatment with dupilumab in the past.
6. Patients who have used any the following treatments within 4 weeks before the baseline visit
   a. Systemic corticosteroids
   b. Immunosuppressive/immunomodulating drugs (eg, alitretinoin, cyclosporine, mycophenolate mofetil, IFN-γ, systemic Janus kinase inhibitors, azathioprine or methotrexate)
   c. Phototherapy (including localized psoralen and UVA [PUVA] or narrow band ultraviolet B [UVB] on hands and/or feet).
7. Treatment with biologics, other than dupilumab, as follows:
   a. Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte and CD 19+ lymphocyte count returns to normal, whichever is longer
   b. Other biologics: within 5 half-lives (if known) or 16 weeks prior to the baseline visit, whichever is longer
8. Treatment with TCS or TCI or crisaborole or topical Janus kinase (JAK) inhibitor within 2 weeks before the baseline visit on the hand and foot.
9. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit.
10. Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit.
11. Planned or anticipated use of any prohibited medications and procedures during study treatment.
12. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency as judged by the investigator.
13. Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity.
14. With a current diagnosis of hepatitis B viral infection at the time of screening as evidenced by
    a. Positive hepatitis B surface antigen (HBsAg) or
    b. Positive total hepatitis B core antibody (HBcAb) confirmed by positive HBV DNA

NOTE:

Patients who have gained immunity for hepatitis B virus infection after vaccination (patients who are HBsAg negative, hepatitis B surface antibody [HBsAb] positive, and HBcAb negative) or after natural infection (patients who are HBsAg negative, HBsAb positive, and HBcAb positive) are eligible for the study. These patients will be allowed to enroll into the study but will be followed using routine clinical and liver function tests.

In case of results showing HBsAg negative, HBsAb negative, and HBcAb positive, a HBV DNA testing will be performed prior to randomization to rule out a false positivity and to confirm current infection. Patients who are HBcAb positive and HBV DNA negative will be eligible to enroll in the trial.

15. With a current diagnosis of hepatitis C viral infection at the time of screening as evidence by
    a. Positive HCV Ab AND
    b. Positive HCV RNA
16. On current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis, or hepatic failure, or has evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal (ULN) during the screening period.
17. Presence of any 1 or more of the following abnormalities in laboratory test results at screening:
    a. Platelets $\leq 100 \times 10^3/\mu L$
    b. Neutrophils $< 1.5 \times 10^3/\mu L$
18. Diagnosed active endoparasitic infections. Patients with suspected or high risk of endoparasitic infection will be excluded, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
19. Presence of skin comorbidities on hand and foot that may interfere with study assessments. This includes, but is not limited to palmoplantar psoriasis, palmoplantar keratoderma, lichen planus, pityriasis rubra pilaris, herpes simplex, erythema multiforme, tinea mannum/tinea pedis, scabies, granuloma annulare.
20. History of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
21. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to patients with short life expectancy, patients with uncontrolled diabetes (HbA1c ≥9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, Eosinophilic granulomatosis with polyangitis (EGPA), lupus, inflammatory bowel

disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, hepato-biliary, metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents.

22. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents.
23. History of alcohol or drug abuse within 2 years before the screening visit.
24. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
25. Patient is a member of the investigational team or his/her immediate family.
26. Pregnant or breastfeeding women or planning to become pregnant or breastfeed during the patient's participation in this study.
27. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device; intrauterine hormone-releasing system
    c. bilateral tubal ligation
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)
    e. and/or sexual abstinence†, ‡.

    *Women of childbearing potential are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

†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 drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

f. ‡Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patient who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.4.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study or study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

- Dupilumab, administered SC Q2W
  - in adults; dupilumab 300 mg, after a loading dose of 600 mg on day 1, irrespective of body weight
  - in adolescents; Body weight ≥60 kg, dupilumab 300 mg, after a loading dose of 600 mg on day 1, body weight <60 kg, dupilumab 200 mg, after a loading dose of 400 mg on day 1.
- Matching placebo, administered SC Q2W

Randomization is discussed in Section 8.6.

Study drug will be administered by SC injections. Subcutaneous injection sites of study drug should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Background Treatment

All patients are required to apply moisturizers on their hands and feet at least twice daily during the screening period. It is recommended that patients continue the use of moisturizers throughout the study (all 28 weeks where applicable). All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study. Patients may continue using stable doses of such moisturizers if initiated before the screening visit. It is recommended that the moisturizers used be free of additives, fragrances, perfumes, and other potentially sensitizing agents. Moreover, it is recommended that the moisturizers not contain any compound with known anti-itch effect (such as pramoxine, lidocaine, prilocaine, capsaicin etc.).

NOTE: In patients with lesions of AD on parts of the body other than hands and feet, emollients are permitted but are not required as background medication for other body regions.

8.3. Rescue Treatment

Rescue treatment for worsening of AD of hands and feet may be provided to study patients at the discretion of the investigator in the study. The use of rescue treatment is only allowed after day 14 of the study. Investigators will be required to perform an IGA for hands and feet assessment prior to starting rescue treatment and initiate rescue treatment only in patients who have an IGA hand and foot score ≥3. If possible, investigators are encouraged to consider rescue initially with topical treatment (high potency or ultra-high potency TCS, TCIs, crisaborole, topical JAK inhibitors) and to escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. Rescue treatment for the topical therapies should be used as per prescribing information and local guidelines. Patients may continue study treatment if rescue consists of topical medications.

Investigators can also use systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (alitretinoin, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, JAK inhibitors etc) for rescue in patients with worsening of AD of hands and feet. Patients may continue study treatment if rescue consists of these systemic therapies, based upon discretion of investigator. All patients will be asked to complete the scheduled study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety laboratory tests) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary. For the purpose of the efficacy responder analysis, a pre-specified algorithm will be used to classify rescue (details in the SAP). In addition, a blinded review of all post-baseline medications to adjudicate rescue treatment, based on medical judgment, will be performed to adjudicate rescue. Data from patients

who receive rescue treatment as per this adjudication during the study will be treated for efficacy analysis purposes as outlined in Section 11.4.3.

Note: During the study, patients might also experience flare of AD lesions on parts of the body other than hands and feet. Rescue treatment (in addition to low to medium TCS that are permitted during the study) will be allowed after day 14 of the study. It is recommended that investigators manage these flares using topical therapies, unless the use of systemic therapies is deemed necessary based on severity and extent of flare as determined by the investigator. High/ultra-high potency TCS/TCIs/crisaborole can be used in such situations. The hands and feet should be spared from the use of these topical therapies, unless there is evidence of exacerbation of lesions on hands and feet as per clinical judgment of the investigator. In case systemic corticosteroids or non-steroidal systemic immunosuppressive drugs are used for controlling flare in AD lesions on parts of the body other than hands and feet, the study drug may be continued, based upon discretion of investigator.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2 .

8.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction [eg, Hy's law is met (FDA, 2009)]
- Patient or parent/legal guardian withdraws assent or consent
- Diagnosis of a malignancy during study other than non-melanoma skin cancer or carcinoma in situ that is considered curable by local surgery
- Any infection that is opportunistic, such as TB and other infections whose nature or course may suggest an immunocompromised status
- Severe laboratory abnormalities assessed as related to study drug:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$

- ALT and/or AST values >3 × ULN with total bilirubin >2 × ULN, excluding confirmed Gilbert's Syndrome
- Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks)

NOTE:

If the laboratory abnormality is considered causally related to study drug, study treatment will be permanently discontinued. In cases in which a causal relationship to study drug can be reasonably excluded, (ie, an alternative cause is evident), study treatment will be suspended but it may be resumed when the laboratory abnormality is sufficiently normalized. A decision to resume study treatment will be made jointly by the investigator and medical monitor (medical monitor's written approval is required).

- Treatment with a live attenuated vaccine (refer to Section 8.10.1 for details)
- Treatment with an investigational drug

The investigator may discontinue 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.

8.4.2.2. Reasons for Temporary Discontinuation of Study Drug

- Clinically important laboratory abnormalities, such as:
  - ALT or AST >3 × ULN
  - Neutrophil count <1.5 × 10^3/μL but >0.5 × 10^3/μL
  - Platelet count ≤100 × 10^3/μL but >50 × 10^3/μL

After the condition leading to suspension of dosing resolves, study treatment may resume at the discretion of the investigator in consultation with the medical monitor. A decision to temporarily discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor.

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.

8.5. Management of Acute Reactions

8.5.1. Acute Injection Reactions

8.5.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4 .

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.5.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4

8.6. Method of Treatment Assignment

Approximately 130 patients will be randomized in a 1:1 ratio to receive either dupilumab or placebo according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

Randomization will be stratified by age (adults vs. adolescents), disease severity (IGA hand and foot 3 vs. 4), and geographic region (United States versus Japan versus other countries). Randomization will be capped for the adults at approximately 100.

Information on the anatomical area of involvement (hands only vs. hands and feet vs. feet only) will be collected at baseline prior to randomization. The number of patients with hands only involvement will be capped at approximately 100.

8.7. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody and drug concentration results will not be communicated to the sites, and the sponsor's blinded operational team will not have access to results associated with patient identification until after the database is locked.

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded (Section 8.4.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient.
  - The IVRS/IWRS will provide the treatment assignment to the investigator and will notify Regeneron of the unblinding transaction.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

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

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.9.2. Supply and Disposition of Treatments

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

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication.

- dispensed to each patient
- returned from each patient (if applicable), and

- disposed of at the site or returned to the sponsor or designee.

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

8.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.10. Concomitant Medications and Procedures

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

8.10.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited during the study treatment period (through week 16):

- Topical corticosteroids on hand and foot (may be used as rescue)
- Topical calcineurin inhibitors on hand and foot (may be used as rescue)
- Topical crisaborole on hand and foot (may be used as rescue)
- Topical JAK inhibitors on hand and foot (may be used as rescue)
- Systemic immunosuppressive/immunomodulating drugs (including, but not limited to alitretinoin, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate, IFN-γ, systemic JAK inhibitors, or other biologics) (may be used as rescue)
- Systemic corticosteroids (may be used as rescue)
- Treatment with an investigational drug
- Treatment with a live (attenuated) vaccine

Chickenpox (varicella)	Oral typhoid
FluMist-Influenza	Rubella
Intranasal influenza	Smallpox (vaccinia)
Measles (rubeola)	Yellow fever
Measles-mumps-rubella combination	Bacille Calmette-Guerin
Measles-mumps-rubella-varicella combination	Rotavirus
Mumps	Varicella zoster (shingles) (use of Zostavax is prohibited as it is live attenuated; use of Shingrix is allowed as it is non-live)
Oral polio (Sabin)	

Note: If at screening visit, there is an anticipated need for use of live vaccines during the study, the patient should receive the vaccine during the screening period at least 4 weeks prior to baseline visit.

The following concomitant procedures are prohibited during study treatment through week 16:

- Major elective surgical procedures
- Phototherapy (ultraviolet A [UVA], UVB, narrowband UVB [nbUVB], high dose UVA, and PUVA), localized PUVA or narrow band UVB on hands and/or feet
- Tanning in bed/booth

8.10.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 8.10.1, treatment with concomitant medications are permitted during the study. Topical treatments used for AD lesions on parts of the body other than the hands and feet will be permitted. This includes low to medium potency TCS (high potency/ultra-high TCS are prohibited), TCIs and crisaborole. In order to avoid confounding of assessment of AD lesions on the hands, patients will be asked to either a) use gloves or tongue depressors if applying themselves or b) have a caregiver apply topical treatments on these lesions. In addition, use of contraceptives and basic skin care (cleansing and bathing including bleach baths) as well as treatment with emollients, topical anesthetics, antihistamines, topical and systemic anti-infective medications for any duration are permitted.

Medications used to treat chronic disease such as diabetes and hypertension 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.

In patients with lesions of AD on parts of the body other than hands and feet, emollients are permitted but are not required as background medication for other body regions.

8.10.3. Skin Protection Measures

Patients will be required to follow routine skin protection measures throughout the duration of the screening period in order to be eligible for the study. It is recommended that patients continue with these measures during the duration of the study. These measures will include the following:

- Avoidance of identified irritants for hand and foot dermatitis.
- Using protective gloves when performing wet work. It should be ensured that protective gloves should be intact and clean and dry inside. When protective gloves are used for a long period of time, cotton gloves should be worn underneath. Latex is best avoided for risk of contact urticaria and/or ACD.
- Washing hands in lukewarm (not hot) water and to rinse and dry hands thoroughly after washing.
- Minimize excessive hand washing with soaps and substitute with alcohol disinfection when hands are not visibly dirty.
- Application of moisturizers, preferably those which are free from fragrances and with preservatives having the lowest allergen potential.

The site staff will instruct the patients on further skin protection measures, if applicable.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 1: Schedule of Events

Study Period	**Screening**		**Treatment Period**									**Follow-up**		
Study Milestone			**BL**								**EOT**	**EOS**		
In-Clinic Visit (V)* or Phone Visit (PV)	V1	V1a	V2	V3	V4	PV5[1]	V6	PV7[1]	V8	PV9[1]	V10	V11	Unscheduled visit[2]	ET visit
Week (W)				W2	W4	W6	W8	W10	W12	W14	W16	W28		
Study Day (D)	D-56 to D-1		D1	D15	D29	D43	D57	D71	D85	D99	D113	D197		
Visit Window in Days				±3	±3	±3	±3	±3	±3	±3	±3	±4		
Screening/ Baseline														
Informed consent/assent	X													
Informed consent/assent for optional genomic sub-study[3]	X													
Informed consent/assent for optional future biomedical research sub-study[4]	X													
Informed consent/assent for optional use of photographs for educational/marketing purposes (selected study sites only)	X													
Inclusion/Exclusion criteria	X		X											
Patch testing[5,6,7,8]		X												
Medical History	X													
History of exposure to irritants relevant to hand and foot dermatitis	X													
Assign disease morphology[9]			X											
Assign anatomical area of involvement[10]			X											

Study Period	**Screening**		**Treatment Period**									**Follow-up**		
Study Milestone			**BL**								**EOT**	**EOS**		
In-Clinic Visit (V)* or Phone Visit (PV)	V1	V1a	V2	V3	V4	PV5[1]	V6	PV7[1]	V8	PV9[1]	V10	V11	Unscheduled visit[2]	ET visit
Week (W)				W2	W4	W6	W8	W10	W12	W14	W16	W28		
Study Day (D)	D-56 to D-1		D1	D15	D29	D43	D57	D71	D85	D99	D113	D197		
Visit Window in Days				±3	±3	±3	±3	±3	±3	±3	±3	±4		
Demographics	X													
Randomization			X											
Patient diary training[11]	X		X											
Treatment														
Injection training/ observation[12]			X	X	X		X		X					
Administration of study drug			X[13]	X	X	X	X	X	X	X				
Patient dosing diary completion						X		X		X				
Patient counseling for diary completion			X	X	X		X		X					
Study drug dispensation[14]					X		X		X				X	X
Study drug accountability[14]							X		X		X			
Con meds/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin protection measures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy[15]														
Patient assessment of hand and foot pruritus intensity using NRS via diary (daily)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient assessment of hand and foot skin pain and sleep NRS[16]	X	X	X	X	X						X	X		

Study Period	**Screening**		**Treatment Period**									**Follow-up**		
Study Milestone			**BL**								**EOT**	**EOS**		
In-Clinic Visit (V)* or Phone Visit (PV)	V1	V1a	V2	V3	V4	PV5[1]	V6	PV7[1]	V8	PV9[1]	V10	V11	Unscheduled visit[2]	ET visit
Week (W)				W2	W4	W6	W8	W10	W12	W14	W16	W28		
Study Day (D)	D-56 to D-1		D1	D15	D29	D43	D57	D71	D85	D99	D113	D197		
Visit Window in Days				±3	±3	±3	±3	±3	±3	±3	±3	±4		
IGA (hand and foot), mTLSS, hand and feet area involvement, HECSI[17]	X		X	X	X		X		X		X	X	X	X
EQ-5D[18], WPAI+CIQ[18]	X		X		X						X	X		X
PGIS[18], QOLHEQ[17,18]	X		X	X	X		X		X		X	X		X
PGIC[18]				X	X		X		X		X	X		X
IGA (global)[19], EASI[19]			X		X						X	X		X
Photograph areas of atopic hand or foot dermatitis (select sites)			X								X	X		X
Safety														
Weight	X		X								X	X		X
Height	X										X			
Vital signs	X		X[13]								X	X	X	X
Physical examination	X										X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[20]**														
Hematology	X		X								X	X	X	X
Chemistry	X		X								X	X	X	X
Urinalysis	X		X								X	X	X	X
Pregnancy test, WOCBP only	Serum		Urine				Urine		Urine		Urine	Urine	Urine	Urine

Study Period	**Screening**		**Treatment Period**									**Follow-up**		
Study Milestone			**BL**								**EOT**	**EOS**		
In-Clinic Visit (V)* or Phone Visit (PV)	V1	V1a	V2	V3	V4	PV5[1]	V6	PV7[1]	V8	PV9[1]	V10	V11	Unscheduled visit[2]	ET visit
Week (W)				W2	W4	W6	W8	W10	W12	W14	W16	W28		
Study Day (D)	D-56 to D-1		D1	D15	D29	D43	D57	D71	D85	D99	D113	D197		
Visit Window in Days				±3	±3	±3	±3	±3	±3	±3	±3	±4		
HIV, HBsAg, HBsAb, HBcAb[21], HBV DNA[22], Hep C Ab[23], HCV RNA[24], TB[25]	X													
Optional DNA sample[3]			X											
PK and ADA Sample[20]														
Functional dupilumab PK sample			X								X	X	X	X
Anti-dupilumab antibody sample			X								X	X	X	X

ADA=anti-drug antibody; BL=baseline; D= Day; EASI=Eczema Area and Severity Index; EOS=end of study; EOT=end of treatment; ET=early termination; FBR = future biomedical research HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HECSI=Hand Eczema Severity Index; HIV=human immunodeficiency virus; IGA=Investigator Global Assessment; mTLSS=Modified Total Lesion Sign Score; NRS=Numerical Rating Scale; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic; PV=phone visit; TB=tuberculosis; V=visit; W=week; WPAI+CIQ=WPAI plus Classroom Impairment Questionnaire; WOCBP=women of childbearing potential.

9.1.1. Footnotes for the Schedule of Events Table

*Phone visits/virtual visits/telemedicine visits/home visits by skilled staff should be considered in case of lack of availability of site staff and/or patients to come to site for in-clinic visits **due to COVID-19 pandemic**. The following investigator-performed assessments, if feasible, should be performed using telemedicine/virtual visits/home visits by skilled staff:

i. IGA (hand and foot)

ii. mTLSS

iii. Hand and feet area involvement

iv. HECSI

Site staff should make every effort to conduct telephone interviews to complete the following questionnaires:

i. EQ-5D

ii. WAPI + CIQ

iii. PGIS

iv. QOLHEQ

v. PGIC

Site staff should also collect information on AEs and concomitant medications.

Site staff should conduct the telephone interviews on the date of scheduled site visit by following an interview guide provided by the sponsor. Patient responses from the interviewer-administered questionnaires will be captured by the site staff directly into the tablet OR onto a paper-copy printout of the questionnaire screenshots. In case telephone interviews cannot be conducted, the questionnaires may be sent by mail/email to the patient's home. Questionnaires should be completed by patients and returned to the site.

1. The site will contact the patient by telephone to conduct these visits. The patient or caregiver (in case of adolescents, if applicable) may administer study drug on these days. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and to document any related issues. Site staff will also remind the patients to either a) use gloves or tongue depressors if applying themselves or b) have a caregiver apply, when patients are using TCS treatment on lesions of AD other than hands and feet.
2. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason (eg, before a rescue). The assessments and procedures performed during an unscheduled visit will depend upon the reason for the visit. During an unscheduled visit, any of the study procedures noted may be performed, but not all are required. If the unscheduled visit is due to an AE, collect samples for PK and ADA analysis

3. For patients who decide to participate and provide a specific written informed consent/assent for the optional genomics sub-study (DNA sample collection). DNA sample should be collected at the day 1 visit (predose) but can be collected at any visit during the study.
4. FBR samples will be optional. No additional samples are collected for patients who sign the FBR consent. FBR analyses will be performed on leftover biological samples (PK and ADA).
5. Patch testing with a standard series of allergens will be carried out in all patients unless there is documented evidence that patient has been previously patch tested with the same series (or an expanded series which contains all the allergens in the standard series tested in this study) within last 3 years and the investigator determines from clinical judgment that further patch testing is unnecessary. In that case, the results from the previous patch test will be used for determining eligibility
6. In addition to standard baseline series, additional patch testing with expanded series and/or patient personal products may be carried out if deemed necessary by the investigator
7. Patients will need to visit the site at least 3 times during the screening period for the conduct of patch tests (day of application, reading of results at day 2, reading of results at day 3 to day 7). In some patients a reading after 7 to 10 days may be taken when the clinical history strongly supports sensitization
8. Patients will need to discontinue topical and systemic therapies for AD for a certain period prior to patch testing. Please refer to Section 9.2.1.1 for further details on patch testing
9. Investigators will assign patients to the following disease morphology for each anatomical area of hand and foot involvement:
    - Hyperkeratotic
    - Dyshidrotic
    - Pulpitis
    - Nummular eczema
    - Chronic dry fissured forms of eczema
    - Unspecified

It is acknowledged that a mixed pattern might be present in some patients. Investigators should identify the predominant morphology in such cases and assign patients accordingly.

Investigators will also assign an overall disease morphology which will be based upon the disease morphology of the anatomical area with most severe disease (in some cases, a different morphology may be present in hands vs. feet). In these scenarios, investigators should assign morphology based on the region with higher severity of involvement (hands or feet).

10. Investigators will assign patients to the following anatomical areas of involvement:
    - Hands only
    - Hands and feet

- Feet only

11. Training of patients regarding completion of diary to record a) administration of each dose of drug outside the clinic by patient, b) completion of assessment of pruritus using NRS scale, c) completion of assessment of pain using NRS scale, d) completion of assessment of sleep loss using NRS scale, and e) twice daily application of emollients
12. Patients or caregivers (in case of adolescents, if applicable) will be trained on how to administer study drug under observation by site staff to ensure correct administration technique. This would enable administration at home in between clinic visits.
13. Patients will be monitored at the study site at visit 2 for a minimum of 30 minutes after study drug administration. Vital signs (blood pressure, respiratory rate and pulse rate) and AE assessments will also be assessed at 30 minutes (+/- 10 minutes) post-injection, in addition to pre-dose assessment.
14. Starting at visit 4, study drug will be dispensed to the patient for the dose that will be administered at home before the next clinic visit. Patients will return the study kit box (for prefilled syringes) at each subsequent clinic visit. At these in-clinic visits, sites will perform accountability assessment for the study drug that the patients have returned to the site. In case of lack of availability of site staff and/or patients to come to the site for in-clinic visits due to the COVID-19 pandemic, the sponsor may implement processes for direct-to-patient shipment of study drug.
15. Assessments/procedures should be conducted in the following order: patient-reported outcomes, investigator assessments, safety and laboratory assessments, administration of study drug.
16. Pain and sleep quality will be assessed daily throughout the screening period, the 7 days leading up to the week 2 visit, the 7 days leading up to the week 4 visit, the 7 days leading up to the week 16 visit, and 7 days leading up to the week 28 visit. Patients will complete a daily diary on these days to record skin pain and sleep quality NRS.
17. The HECSI and QOLHEQ will only be performed in patients with presence of hand dermatitis at baseline
18. The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).
19. Standard assessments for AD lesions over the whole body, not just limited to hands and feet. As part of these assessments, sites will answer the question: Does the patient have AD lesions outside the hands and/or feet? These assessments will only be performed in patients who have AD lesions outside their hands and feet.
20. Samples will be collected before the injection of study drug. Serum samples will be collected for the determination of dupilumab concentration in and for the immunogenicity assessment of dupilumab. In the event of suspected serious adverse events (SAEs), such as anaphylaxis or hypersensitivity, additional PK and ADA samples may be collected at or near the event. Samples positive in the ADA assay will be analyzed in the NAb assay.

** Alternate measures for laboratory testing should be considered in case of lack of availability of site staff and/or patients to come to the site for in-clinic visits due to the COVID-19 pandemic. Assessments, including but not limited to, which can be performed are as follows:

a. Hematology
b. Chemistry
c. Urinalysis
d. Pregnancy test

21. In case of results showing HbsAg negative, HbsAb negative and HbcAb positive, HBV DNA testing will be performed prior to randomization to rule out a false positivity and to confirm current infection.
22. Only performed in patients whose serology results show HbsAg negative, HbsAb negative and HbcAb positive.
23. In case of results showing positive hepatitis C antibody (Hep C Ab), an HCV RNA will be performed to rule out a false positivity and to confirm current infection.
24. Only performed in patients whose serology results show positive Hep C Ab.
25. TB testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.

9.1.2. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 16) will be asked to return to the clinic for an early termination visit consisting of the early termination assessments described in Table 1.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

9.2. Study Procedures

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

1. Patient Reported Outcomes
2. Investigator assessments (performed only by adequately trained and qualified investigators or sub-investigators; it is recommended that the same investigator or sub-investigator perform all the evaluations for a given patient throughout the entire study period)
3. Safety and laboratory assessments (including sample collection for ADA, PK, and optional DNA).
4. Administration of study drug

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Medical History
- Detailed occupational, social, and personal history relevant to hand and foot dermatitis
- Demographics
- Inclusion/Exclusion criteria, including hepatitis and HIV serology, and TB (if required per local regulation)
- Patch Testing
- Patient diary training

9.2.1.1. Patch Testing

Patch testing with a standard series of allergens will be conducted during the screening period for determining eligibility. Patch testing should normally be conducted after other screening procedures (eg, lab testing) have been completed and eligibility for the study confirmed. Patients need to discontinue therapies for AD before the patch testing is conducted. The wash out period will be as follows:

1. 1 week for TCS/TCI /topical JAK inhibitor/crisaborole application (this application will not be allowed only on the region of the body where patch testing is planned which in most cases would be the upper back)
2. 4 weeks for UVA and UVB
3. 4 weeks for oral corticosteroids
4. 4 weeks for other systemic immunomodulators such as cyclosporine (CsA), mycophenolate mofetil (MMF), methotrexate (MTX), Alitretinoin, systemic JAK inhibitors etc.

The standard series used will vary based upon the region of conduct of the study, eg, TRUE test in the US, The TRUE test and an additional panel of allergens (provided in the study manual) which are not included in TRUE test but are commonly implicated in causing ACD of hands and feet in patients in the EU, and patch test panel (S) in Japan. In case other countries/regions are added to the study, country specific patch test series may be used as applicable. In case of patients who have had patch testing with the same country-specific series of allergens within 3 years prior to screening visit, the patch testing does not need to be repeated and results from the previous patch test can be used for study purposes.

In addition, patch testing with extended baseline series, supplemental series and/or personal products may be carried out as per clinical judgment of investigator.

Patients will be called to the site for 3 visits for the patch testing

1. Appointment 1 (day 0): Application of patch tests
2. Appointment 2 (reading of results at day 2): the patches will be removed, and reading will be taken 20 to 30 minutes after removal of the patches.
3. Appointment 3 (reading of results at day 3 to day 7): A second reading will be taken

In some patients a reading after day 7 may be taken when the clinical history strongly supports sensitization. This is especially relevant for contactants such as metals (nickel sulfate, gold sodium thiosulfate, palladium chloride, potassium dichromate, cobalt chloride), some antibiotics (neomycin), TCS (tixocortol-21-pivalate, budesonide), and dyes (para-phenylenediamine).

The patch test should be applied on normal appearing skin free from skin diseases such as AD. The upper back is preferred site for the application of patch tests. In case not suitable for patch testing, or is fully used already, the upper parts of the arm may be used.

The patch tests will be read using the globally recognized the ICDRG criteria:

Symbol	**Morphology**	**Assessment**
-	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction

For the purpose of this study, a score of 1+ and above will be considered a positive result. The investigators should be careful to exclude irritant reactions which typically appear within the first 48 hours and tend to disappear (decrescendo effect) by 96 hours, whereas allergic reactions tend to increase (crescendo effect). Moreover, the morphology of these irritant reactions can differ from allergic reactions with presence of necrosis and bullae.

The history and physical examination must be correlated with the result of the PT to establish clinical relevance. A positive PT may be clinically relevant depending on current or past exposures.

Current relevance will be defined as definite if the PT or use test with the suspected material is positive This occurs if an allergen is found in the patient's environment (example: fragrance in the patient's personal care products), the dermatitis corresponds to the point of contact with allergen (face), and the dermatitis improves with avoidance or recurs with rechallenge. Relevance is probable if the antigen is present in known skin contactants and the clinical presentation is consistent with that exposure. This can occur if the allergen is found in the patient's environment and the dermatitis corresponds to the point of contact with allergen but follow-up information on improvement with avoidance or rechallenge not available. Relevance is possible if skin contact with materials known to contain the allergen was likely. Past relevance is considered if the PT is positive but the exposure was in the past, and not the present.

Further instructions on patch testing and guidance to the patients will be provided in the study manual.

9.2.2. Efficacy Procedures

9.2.2.1. Investigator Global Assessment of Hand and Foot

The IGA for hands and feet is an adaptation of the physician global assessment instrument which has been previously used in registrational studies in hand dermatitis (Ruzicka, 2008). The global IGA for generalized AD lesions throughout the body has been previously used in dupilumab studies in patients with AD (Simpson, 2016).

Investigators will be asked to assess the severity of signs of disease on hands and feet on this scale. It is important that this assessment be limited to only the hands and feet and not be influenced by severity of AD lesions on other parts of the body. The IGA score will be assessed at time points according to Section 9.1 .

The IGA is provided in Appendix 2 .

9.2.2.2. Modified Total Lesion Sign Score for Hands and Feet

The Modified Total Lesional Sign Score is adapted for hands and feet; which has been previously used in registrational studies in hand dermatitis (Ruzicka, 2008). A similar instrument, Global Individual Sign Score, has been previously used for assessment of severity of generalized AD lesions in dupilumab studies in patients with AD (Simpson, 2016).

It is important that this assessment be limited to only the hands and feet and not be influenced by severity of AD lesions on other parts of the body. The mTLSS for hands and feet will be assessed at time points according to Section 9.1 .

The mTLSS for hands and feet is provided in Appendix 3

A responder threshold (currently unknown) for mTLSS in the study population will be determined using blinded interim data gathered from this study utilizing an anchor-based approach. Both dynamic responder definition (eg, change scores) and static severity bands (eg, none, mild, moderate, severe) will be explored. Treatment arms will be pooled to perform the analysis in a blinded fashion. Analyses using this responder threshold will be conducted to help interpretation of the prespecified endpoints for the mTLSS. The methodology to be used for determining this responder threshold will be specified in the psychometric analysis plan and the determined responder threshold will be specified in the SAP.

9.2.2.3. Hand and Foot Pruritus Numerical Rating Scale

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their hand and foot pruritus (itch) during a 24-hour recall period.

Patients will be instructed on using the patient diary to record their Pruritus NRS score at the screening and baseline visits. Patients will complete the rating scale DAILY according to the time points in Table 1. Clinical sites will check and remind patient to complete the diary at each visit. The pruritus NRS score will be calculated as the average of the last 7 days with a minimum of 4 daily scores.

9.2.2.4. Hand and Foot Skin Pain Numerical Rating Scale

Hand and foot skin pain will be measured using a skin pain NRS.

Clinical sites will check and remind the patient to complete the scale according to the time points in Table 1. Patients will be instructed on using the scale to record their skin pain score at the screening visit. Patients will complete the rating scale DAILY throughout the screening period, for the 7 days prior to the week 2 visit, for the 7 days prior to the week 4 visit, and for the 7 days prior to the week 16 visit. Clinical sites will check patient data collected using an e-diary for protocol compliance and remind patients to complete their e-diary throughout the study.

9.2.2.5. Sleep Numerical Rating Scale

Sleep quality will be measured using a sleep quality NRS. This is an 11-point scale (0 to 10) in which 0 indicates worst possible sleep while 10 indicates best possible sleep. The patients will be asked to select the number that best describes the quality of their sleep during the previous night.

Clinical sites will check and remind the patients to complete the scale according to the time points in Table 1. Patients will be instructed on using the scale to record their sleep quality score at the screening visit. Patients will complete the rating scale DAILY throughout the screening period, for the 7 days prior to the week 2 visit, for the 7 days prior to the week 4 visit, and for the 7 days prior to the week 16 visit. Clinical sites will check patient data collected using an e-diary for protocol compliance and remind patients to complete their e-diary throughout the study.

9.2.2.6. Hand and Foot Area Involvement of Atopic Dermatitis

This assessment will be performed at time points according to Section 9.1 . The hand and foot area assessment tool is provided in the study reference manual.

9.2.2.7. Patient Global Impression of Severity

The PGIS will be assessed at time points according to Table 1. This instrument is provided in the study reference manual.

9.2.2.8. Patient Global Impression of Change

The PGIC will be assessed at time points according to Table 1. This instrument is provided in the study reference manual

9.2.2.9. Hand Eczema Severity Index

The HECSI is similar to scoring systems in AD (EASI) and Psoriasis vulgaris (PASI) in incorporating both the extent and the intensity of the disease. Each hand is divided into 5 areas [fingertips, fingers (except the tips), palms, back of hands and wrists]. For each of these areas the intensity of the 6 following clinical signs: erythema, induration /papulation, vesicles, fissuring, scaling and oedema is graded on the following scale: 0, no skin changes; 1, mild disease; 2, moderate, and 3, severe. For each location (total of both hands) the affected area is given a score from 0 to 4 (0, 0%; 1, 1 to 25%; 2, 26 to 50%; 3, 51 to 75%, and 4, 76 to 100%) for the extent of clinical symptoms. Finally, the score given for the extent at each location is multiplied by the total sum of the intensity of each clinical feature, and the total sum called the HECSI score is calculated,

varying from 0 to a maximum severity score of 360 points. The HECSI has been previously validated in patients with hand dermatitis (Held, 2005).

The HECSI will only be performed in patients with presence of hand dermatitis at baseline. This assessment will be performed at time points according Section 9.1 . The HECSI is provided in the study reference manual.

The HECSI will be assessed at time points according to Table 1.

The HECSI assessment tool is provided in the study reference manual.

9.2.2.10. Quality of Life in Hand Eczema Questionnaire

The QoLHEQ will be assessed at time points according to Table 1

The QoLHEQ is provided in the study reference manual.

9.2.2.11. Eczema Area and Severity Index

This assessment is not limited to just evaluation of hands and feet lesions, but will assess severity of AD lesions across the body. This assessment will only be performed in patients who have AD lesions outside their hands and feet.

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin, 2001). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

The EASI will be assessed at time points according to Table 1.

The EASI assessment tool is provided in the study reference manual.

9.2.2.12. Investigator's Global Assessment

This assessment is not limited to just evaluation of hands and feet lesions, but will assess severity of AD lesions across the body. This assessment will only be performed in patients who have AD lesions outside their hands and feet.

The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe).

The IGA score will be assessed at time points according to Table 1.

The IGA assessment tool is provided in the study reference manual.

9.2.2.13. Atopic Dermatitis Area Photographs

At select study sites, photographs will be taken of a representative area of atopic hand and foot dermatitis involvement. Subsequent photographs of the same area will be taken at time points according to Table 1.

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

9.2.2.14. Patient-Assessed EQ-5D

This assessment is based on general AD, not only of atopic hand and foot dermatitis.

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

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

The questionnaire will be administered only to the subset of patients who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at time points according to Table 1.

The EQ-5D is provided in the study reference manual.

9.2.2.15. Work Productivity and Activity Impairment Questionnaire Plus Classroom Impairment Questions

The WPAI+CIQ is a self-administered instrument used to assess the impact of disease on productivity. An adaptation of WPAI, the WPAI+CIQ incorporates classroom impairment questions in the original WPAI to assess classroom impairment. The WPAI+CIQ measures work/classroom productivity loss due to general health or a specified health problem in past 7 days. The question can be adapted based on the specific condition of study. For this study, WAPI+CIQ-AHFD will be used to capture the impairment to work productivity/classroom impairment and activity due to atopic hand and foot dermatitis. The WPAI+CIQ yields 4 types of scores: absenteeism (work/classroom time missed), presenteeism (impairment at work/classroom or reduced on-the-job/classroom effectiveness), work/classroom productivity loss (overall work/classroom impairment divided by absenteeism plus presenteeism), and activity impairment. All scores range from 0 to 100% with 100% indicating total work/classroom productivity impairment and 0 no impairment at all.

The WPAI+CIQ will be administered to every patient. Depending on whether the patients are currently employed or attending classes, the patients will answer the applicable questions in WAPI components or CIQ components or both.

The WPAI+CIQ will be administered at time points according to Table 1

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs (including pulse rate, sitting blood pressure, body temperature, and respiratory rate) will be collected pre-dose at time points according to Table 1.

At the first 3 administrations of study drug, sitting blood pressure, respiratory rate and pulse rate will also be assessed at 30 minutes (+/- 10 minutes) post-injection.

9.2.3.2. Body Weight and height

Body weight and height will be measured at time points according to Table 1.

9.2.3.3. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.4. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 1. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol[2]
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)[3]
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

1 Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN
2 Low-density lipoprotein and high-density lipoprotein
3 CPK isoenzymes will be measured when CPK >5× the ULN

Hematology

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

Urinalysis

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

Other Laboratory Tests

Serum and urine pregnancy testing will be performed for all female patients of childbearing potential at time points according to Table 1 .

The following tests will be performed at screening: HIV, HBsAg, HBsAb, HBcAb, HBV DNA (only in patients who are HBsAg negative, HBsAb negative, and HBcAb positive), hepatitis C antibody, HCV RNA (only in patients who are HCV Ab positive), and tuberculosis (will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards).

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Measurements

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Table 1.

9.2.5. Immunogenicity Measurements and Samples

Serum samples for ADA and NAb assessment will be collected at time points according to Table 1.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

Not applicable.

9.2.7. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research sub-study will be required to consent to this optional sub-study before samples are banked in long-term storage. The unused PK and ADA samples will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of AD and related diseases, dupilumab and related pathways. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.7.1. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose) but can be collected at a later study visit.

DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of AD and related diseases. These samples will be single-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker responses to dupilumab, other AD clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of AD as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or AD and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period from the time of signing the ICF to the end of study. Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the study) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3 .

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results, if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- SAEs
- **Adverse Events of Special Interest** (serious and nonserious)**:** Adverse events of special interest for this study include the following:
- Anaphylactic reaction
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Refer to the study reference manual for the procedures to be followed.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, 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).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

10.2.5. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs. time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction

- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (dupilumab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for study drug (dupilumab) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the SAP for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4 Analysis variables are listed in Section 5. Handling of missing data due to the COVID-19 pandemic and any additional analyses required to investigate the impact of COVID-19 to understand estimated treatment effect and safety will be detailed in the SAP.

11.1. Statistical Hypothesis

For comparison of dupilumab treatment to placebo, the following hypothesis of the primary endpoint will be tested:

- Null hypothesis: the success rate (where success is proportion of patients achieving an IGA score of 0 or 1 on hand and foot at week 16) is equal between dupilumab and placebo
- Alternative hypothesis: the success rate differs at week 16 between dupilumab and placebo.

11.2. Justification of Sample Size

The planned sample size is approximately 130 patients (65 patients in each treatment arm). This sample size will yield >85% power to detect a treatment difference of 24% in the proportion of patients achieving IGA hand and foot (0, 1) at week 16 between placebo (10%) and dupilumab (34%) at a 2-sided significant level of 5% using Chi-square test and assuming a dropout rate of 10%. The assumed treatment difference of 24% is based on the effect of 26% observed in dupilumab phase 3 monotherapy studies in adult patients with AD and adjusted to account for the potential inclusion of some patients with ACD who would be missed with certain patch testing (ie, TRUE test) at screening.

It is reasonable to assume that the effect size of dupilumab on AD of hands and feet would be similar to that seen in global AD lesions in previously conducted phase 3 trials as the underlying pathophysiology is same. Moreover, a recent observational study to compare effect of dupilumab on hand lesions vs. lesions on other parts of the body found a high degree of concordance in terms of onset of effect and overall effect at week 16 (Oosterhaven, 2018).

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated at randomization (as randomized).

The per protocol set (PPS) includes all patients in the FAS except for those who are excluded because of specified important protocol deviations. A preliminary list of such important protocol deviations is provided below and the final list will be specified in the SAP prior to database lock.

- Entered study even though entry criteria not satisfied
- Received an excluded concomitant treatment
- Received wrong treatment or incorrect dose
- Other treatment compliance

All efficacy variables will be evaluated on the FAS; the primary endpoint will also be evaluated on the PPS. Analysis on the FAS will be considered to be primary.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received any study drug and had at least 1 non-missing ADA result following the first study dose.

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA negative are set to negative in the NAb analysis set).

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

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

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

For all efficacy variables, the analysis will be comparisons of the dupilumab treatment group with the placebo group.

11.4.3.1. Primary Efficacy Analysis

The primary endpoint of proportion of patients achieving an IGA score of 0 or 1 on hand and foot at week 16 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test to assess the difference in the proportion of responders in the FAS adjusting for the randomization stratification factors (age [adults vs. adolescents], disease severity of IGA hand and foot [3 vs. 4], and geographic region [United States versus Japan versus other countries]).

The primary estimand of interest, the intercurrent event(s) strategy, and missing data handling methods for the primary endpoint (binary response) are described in Table 2.

Table 2: Summary of Primary Estimand for Primary Endpoint

Endpoint	Intercurrent Event(s)	Strategy	Missing Data Handling Method
Primary efficacy endpoint (proportion of patients achieving an IGA score of 0 or 1 on hand and foot at week 16)	Rescue treatment	Composite strategy: Patients will be considered as non-responders after such events.	Patient will be considered as non-responder if patient's IGA on hand and foot is missing at week 16 due to patient discontinuation from study or other reasons.
	Treatment discontinuation	Treatment policy strategy: Data collected after the patient discontinued treatment will be included in the analysis.	

To account for use of rescue treatment, patients will be considered as non-responders for all time points subsequent to the use of rescue treatment in the primary analysis. If a patient has missing value with any reason for IGA on hand and foot assessment at week 16, the patient will be classified as a non-responder at week 16.

Sensitivity analysis using the last observation carried forward (LOCF) approach or the worst observation carried forward (WOCF) approach to determine patient's status at week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. The efficacy data will be set to missing after rescue treatment is used, then the LOCF or WOCF method will be used to determine patients' status at week 16.

In addition, the CMH method adjusted by randomization strata will also be performed on all observed data regardless if rescue treatment is used. A patient with missing data will be counted as a non-responder. Other sensitivity analyses may be conducted.

Subgroup analysis (eg, by age group, by anatomical area of involvement [hand involvement only vs. involvement of hand and foot or foot involvement only]) will also be performed.

11.4.3.2. Secondary Efficacy Analysis

The primary estimand of interest, the intercurrent event(s) strategy, and missing data handling methods for the key secondary endpoint (binary response) are described in Table 3.

Table 3: Summary of Primary Estimand for Key Secondary Endpoint

Endpoint	Intercurrent Event(s)	Strategy	Missing Data Handling Method
Key secondary efficacy endpoint (proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥4 from baseline to week 16)	Rescue treatment	Composite strategy: Patients will be considered as non-responders after such events.	Patient will be considered as non-responder if patient's weekly average of daily hand and foot peak Pruritus NRS is missing at week 16 due to patient discontinuation from study or other reasons.
	Treatment discontinuation	Treatment policy strategy: Data collected after the patient discontinued treatment will be included in the analysis.	

Secondary efficacy endpoints that measure binary responses (eg, improvement of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16) will be analyzed in the same fashion as the primary analysis.

Continuous secondary efficacy endpoints (eg, percent change mTLSS for hand/foot lesions from baseline to week 16) will be analyzed using an analysis of covariance (ANCOVA) model for the FAS with treatment group, randomization stratification factors (age [adults vs. adolescents], disease severity of IGA hand and foot [3 vs. 4], and geographic region [United States versus Japan versus other countries]), and relevant baseline measurement included in the model. To account for the impact of rescue treatment on the efficacy effect, patients' efficacy data through week 16 after the rescue treatment use will be set to missing. The missing data for continuous endpoints will be imputed by the pattern-mixture approach where the WOCF approach will be used for the missing due to rescue treatment, AE, and lack of efficacy and the multiple imputation (MI) approach will be used for the missing due to other reasons. The MI Statistical Analysis Software (SAS) procedure with Markov Monte Carlo algorithm will be applied for multiple times. The complete datasets created based on the pattern-mixture approach will be analyzed using the ANCOVA model defined previously, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula.

For the endpoint of percent change in mTLSS for hand/foot lesions from baseline to week 16, the empirical cumulative distribution function (CDF) curves showing response in dupilumab and placebo groups for different responder thresholds will be provided.

All efficacy data will be used for analysis regardless of whether the patient is on study treatment or discontinues the study treatment but remains in the study. In addition, the MI with the ANCOVA model and the ANCOVA model based on LOCF or WOCF imputation method will be performed as the sensitivity analyses. Other sensitivity analysis such as the MI approach with ANCOVA model on all observed data regardless of rescue use will be conducted. Additional details on sensitivity analyses will be provided in the SAP.

11.4.4. Control of Multiplicity

Type I error rate will be controlled using a hierarchical testing procedure for the primary and secondary efficacy endpoints at the 2-sided 0.05 level. The hierarchy order will be specified in the SAP prior to database lock.

11.4.5. Safety Analysis

Safety analysis will be based on the SAF. This includes reported TEAEs, AESIs, and other safety information (eg, clinical laboratory evaluations, vital signs). A summary of safety results for each treatment group will be presented.

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to end of study. The treatment-emergent period includes the 16-week treatment period and 12-week follow-up period.
  - Treatment period: date of the first dose of study drug to week 16 visit date (study day 113 starting from the first dose of study drug if week 16 visit date is unavailable) or early termination date, whichever comes first.
  - Follow-up period: date after week 16 visit date (study day 113 starting from first dose of study drug if week 16 visit date is unavailable) to end of study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment-emergent period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group for overall during the treatment-emergent period, during the 16-week treatment period, and during the follow-up period will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

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

The number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each vital sign variable. The criteria for treatment-emergent PCSV will be defined in the SAP.

Laboratory Tests

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

Number and percentage of patients with a treatment-emergent PCSV will be summarized for each clinical laboratory test. The criteria for treatment-emergent PCSV will be defined in the SAP.

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

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

11.4.5.3. Treatment Exposure

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

(Date of last study drug injection – date of first study drug injection) + 14 days

The number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP. In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, standard deviation, minimums, Q1, medians, Q3, and maximums. A summary of the number of doses by treatment group will be provided as well.

11.4.5.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

Treatment Compliance = (Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) × 100%

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

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of functional dupilumab over time will be summarized by descriptive statistics. No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA and NAb response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative or missing
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 4-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status for samples that are positive in the ADA assay

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers and NAb positivity presented by patient, time point, and dose group will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by dose group and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.5. Timing and Operational Considerations of Statistical Analyses

No interim analysis is planned for this study. The unblinded primary analysis may be performed once all patients in the study have completed the 16-week treatment period. This primary analysis will be considered the final analysis for the primary and secondary efficacy endpoints. Hence there will be no need for alpha adjustment due to the primary analysis.

If a decision is made to perform the primary analysis, in order to maintain study integrity with respect to the post-treatment follow-up visits, safety visits and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the primary analysis and all related activities, restrict other clinical team members and other Sponsor personnel from access to individual patient treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions

for the following post treatment analyses. However, the dedicated team can participate in the analysis following the final database lock.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted, and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC).

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- Digital archive system for photographs
- eCOA instruments/eDiaries/tablet devices for some of the efficacy assessment data

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

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

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection

- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

Adult Patients

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

Pediatric Patients

The principles of informed consent are described in ICH guidelines for Good Clinical Practice.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient and his/her parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient and the

parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients and their parent(s) or legal guardian(s) must be informed of the new information and provide their written consent if they wish the patient to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient's parent(s) or legal guardian(s).

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments),

breach of the applicable laws and regulations, or breach of any applicable ICH guidelines

- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DUPILUMAB IN ADULT AND ADOLESCENT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC HAND AND FOOT DERMATITIS and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. HANIFIN AND RAJKA DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS – MAJOR AND MINOR CRITERIA

Hanifin and Rajka criteria (Hanifin, 1980)

Major criteria:

- pruritus
- dermatitis affecting flexural surfaces in adults and the face and extensors in infants
- chronic or relapsing dermatitis
- personal or family history of cutaneous or respiratory atopy.

Minor criteria:

- features of the so-called "atopic facies": facial pallor or erythema, hypopigmented patches, infraorbital darkening, infraorbital folds or wrinkles, cheilitis, recurrent conjunctivitis, and anterior neck folds
- triggers of atopic dermatitis: foods, emotional factors, environmental factors, and skin irritants such as wool, solvents, and sweat
- complications of atopic dermatitis: susceptibility to cutaneous viral and bacterial infections, impaired cell-mediated immunity, immediate skin-test reactivity, raised serum IgE, keratoconus, anterior subcapsular cataracts
- others: early age of onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris (plugged hair follicles of proximal extremities), hand and foot dermatitis, nipple eczema, white dermatographism, and perifollicular accentuation

APPENDIX 2. INVESTIGATOR GLOBAL ASSESSMENT FOR HAND AND FOOT ATOPIC DERMATITIS

The assessment of the IGA should be based on overall impression of disease severity in hands and feet as per clinical judgment of investigator at time of assessment.

It is not necessary that all signs be present for a patient to be assigned to an IGA category.

Score	Category	IGA Morphological Descriptors
0	Clear	Absence of inflammatory signs of hand and foot atopic dermatitis (erythema, scaling, lichenification, vesicles, fissures, edema).
1	Almost clear	Barely perceptible erythema, barely perceptible scaling, barely perceptible lichenification and/or barely perceptible edema. No vesicles/erosions or fissures.
2	Mild	Slight but definite erythema (pink), slight but definite scaling (fine scales), slight but definite lichenification (slight thickening of the skin with skin markings minimally exaggerated), slight but definite edema (elevation of skin surface discernible only by palpation), slight but definite vesicles/erosions (scattered, small vesicles or erosions) and/or slight but definite fissures (only superficial fissures are present).
3	Moderate	Clearly perceptible erythema (dull red), clearly perceptible scaling (moderately coarse scales), clearly perceptible lichenification (definite thickening of the skin with skin markings clearly exaggerated), clearly perceptible edema (visible elevation of skin surface), clearly perceptible vesicles/erosions (larger vesicles or erosions) and/or clearly perceptible fissures (predominantly superficial fissures but deep fissures may be present)
4	Severe	Prominent erythema (deep dark red), prominent scaling (thick, large scales), prominent lichenification (thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern or with deep furrows), prominent edema (skin surface grossly swollen/elevated), prominent vesicles/erosions (bullae, or densely, clustered vesicles or erosions, often with oozing and crusting) and/or prominent fissures (predominantly deep fissures are present)

Notes:

1. In case of indeterminate cases:
   a. Use extent to guide rating of IGA severity for, example, a patient with prominent erythema and clearly perceptible scaling, with limited extent of disease which would be classified as moderate IGA.
   b. Use severity rating for vesicles and fissures (signs with greater impact on patient's QoL) to step up rating of IGA severity. For example, a patient with clearly perceptible vesicles and slight but definite erythema should be assigned moderate IGA score.
2. Non-inflammatory signs of atopic dermatitis such as post-inflammatory hyper- or hypo-pigmentation, skin dryness etc. should not be used in assessment of IGA.

APPENDIX 3. mTLSS: MODIFIED TOTAL LESION SIGN SCORE FOR HAND AND FOOT ATOPIC DERMATITIS

Instructions:

Assign a score to each of the 6 features (erythema, scaling/flaking, lichenification, vesiculation/erosion, edema, fissures) on a scale of 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe) based on the morphological descriptions of severity provided in the tables below.

A separate score should be assigned for hands and feet.

mTLSS Table for Hand:

Feature	Description of Severity
Erythema	0 = Absent
	1 = Barely perceptible (pink) redness (mild)
	2 = Clearly perceptible (dull red) OR prominent (deep/dark red) redness in limited areas (moderate)
	3 = Prominent (deep/dark red) redness over widespread areas (severe)
Scaling/Flaking[a] [a] Hyperkeratosis is not explicitly included as a separate sign, but hyperkeratosis as seen in hyperkeratotic eczema should be captured by scaling, fissures, and skin thickening	0 = Absent
	1 = Barely perceptible (fine) scales/flakes (mild)
	2 = Clearly perceptible (medium sized scales/flakes that are identifiable as individual scales/flakes on close inspection) scales/flakes OR prominent (thick, large scales/flakes that are easily identifiable as individual scales/flakes) scales/flakes over a limited area (moderate)
	3 = Prominent (thick, large scales/flakes that are easily identifiable as individual scales/flakes) scales/flakes over widespread areas (severe)
Lichenification[b] [b] Palmar hyperlinearity as seen in ichthyosis vulgaris is not to be taken into account while assessing exaggerated skin markings	0 = Absent
	1 = Barely perceptible (slight thickening of the skin with skin markings minimally exaggerated) thickening/exaggerated skin markings
	2 = Clearly perceptible (definite thickening of the skin with skin markings clearly exaggerated) thickening/exaggerated skin markings OR prominent (thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern) thickening/exaggerated skin markings over a limited area (moderate)
	3 = Prominent (thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern) thickening/exaggerated skin markings over widespread areas (severe)
Vesiculation/Erosion	0 = Absent

	1 = Vesicles or erosions affecting up to 10% of the hands (mild)
	2 = Vesicles or erosions affecting between 10%-30% of the hands (moderate)
	3 = Vesicles or erosions affecting more than 30% of the hands (severe)
Edema	0 = Absent
	1 = Barely perceptible (slight elevation of skin surface discernible only by palpation) dermal swelling (mild)
	2 = Clearly perceptible (visible elevation of skin surface) dermal swelling OR prominent (skin surface grossly swollen/elevated) dermal swelling over a limited area (moderate)
	3 = Prominent (skin surface grossly swollen/elevated) dermal swelling over widespread areas (severe)
Fissures	0 = Absent
	1 = Barely perceptible (superficial) fissuring (mild)
	2 = Clearly perceptible (a single deep) fissuring OR prominent (multiple deep) fissuring over limited areas (moderate)
	3 = Prominent (multiple deep) fissuring over widespread areas (severe)

Total hand mTLSS (0-18) _____

mTLSS Table for Foot:

Feature	**Description of Severity**
Erythema	0 = Absent
	1 = Barely perceptible (pink) redness (mild)
	2 = Clearly perceptible (dull red) OR prominent (deep/dark red) redness in limited areas (moderate)
	3 = Prominent (deep/dark red) redness over widespread areas (severe)
Scaling/Flaking[a] [a] Hyperkeratosis is not explicitly included as a separate sign, but hyperkeratosis as seen in hyperkeratotic eczema should be captured by	0 = Absent
	1 = Barely perceptible (fine) scales/flakes (mild)
	2 = Clearly perceptible (medium-sized scales/flakes that are identifiable as individual scales/flakes on close inspection) scales/flakes OR prominent (thick, large scales/flakes that are easily identifiable as individual scales/flakes) scales/flakes over a limited area (moderate)

scaling, fissures, and skin thickening	3 = Prominent (thick, large scales/flakes that are easily identifiable as individual scales/flakes) scales/flakes over widespread areas (severe)
Lichenification[b] [b] Plantar hyperlinearity as seen in ichthyosis vulgaris is not to be taken into account while assessing exaggerated skin markings	0 = Absent
	1 = Barely perceptible (slight thickening of the skin with skin markings minimally exaggerated) thickening/exaggerated skin markings
	2 = Clearly perceptible (definite thickening of the skin with skin markings clearly exaggerated) thickening/exaggerated skin markings OR prominent (thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern) thickening/exaggerated skin markings over a limited area (moderate)
	3 = Prominent (thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern) thickening/exaggerated skin markings over widespread areas (severe)
Vesiculation/ Erosion	0 = Absent
	1 = Vesicles or erosions affecting up to 10% of the feet (mild)
	2 = Vesicles or erosions affecting between 10%-30% of the feet (moderate)
	3 = Vesicles or erosions affecting more than 30% of the feet (severe)
Edema	0 = Absent
	1 = Barely perceptible (slight elevation of skin surface discernible only by palpation) dermal swelling (mild)
	2 = Clearly perceptible (visible elevation of skin surface) dermal swelling OR prominent (skin surface grossly swollen/elevated) dermal swelling over a limited area (moderate)
	3 = Prominent (skin surface grossly swollen/elevated) dermal swelling over widespread areas (severe)
Fissures	0 = Absent
	1 = Barely perceptible (superficial) fissuring (mild)
	2 = Clearly perceptible (a single deep) fissuring OR prominent (multiple deep) fissuring over limited areas (moderate)
	3 = Prominent (multiple deep) fissuring over widespread areas (severe)

Total foot mTLSS (0-18) _____

A total mTLSS score will be calculated as the sum of hand score and foot score:

Total hand and foot mTLSS (0-36) _____

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DUPILUMAB IN ADULT AND ADOLESCENT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC HAND AND FOOT DERMATITIS

Protocol Number: R668-AD-1924

Protocol Version: R668-AD-1924 Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00138022 v1.0

ESig Approval	[redacted] 13-Jan-2021 14:38:51 GMT+0000
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