REGENERON
Biostatistics and Data Management

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STATISTICAL ANALYSIS PLAN
VERSION: 1.0

Clinical Study Protocol 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

Compound:	Dupilumab (REGN668)
Protocol Number:	R668-AD-1924.02
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACD	Allergic Contact Dermatitis
AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
ALT (SGOT)	Alanine aminotransferase
AST (SGPT)	Aspartate aminotransferase
AAS	Anti-Drug Antibody Analysis Set
BUN	Blood urea nitrogen
CRF	Case report form
DLQI	Dermatology Life Quality Index
EASI	Eczema area and severity index
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of study
EOT	End of treatment
ET	Early termination
GB	Great Britain
HLT	High Level Term
ICD	Irritant Contact Dermatitis
ICF	Informed consent form
ICH	International conference on harmonization
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibodies
NRS	Numerical rating scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure

PT	Preferred term
q2w	Once every 2 weeks
q4w	Once every 4 weeks
QOL	Quality of life
qw	Once every week
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SOC	System organ class
SOE	Schedule of events
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of the study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R668-AD-1924 study. This plan will be finalized prior to the database lock for the primary analysis planned when all patients have completed the 16-week treatment period.

1.1. Background and Rationale

Atopic hand and foot dermatitis refers to dermatitis in corresponding anatomical locations in patients with a history of, or presence of concurrent atopic dermatitis (AD) (Agner, 2015). Patients with AD are at a 3 to 4-fold increased risk of hand dermatitis of any etiology as compared to the general population (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 hand and foot dermatitis[1] presents with redness, infiltration, scaling, vesicles, areas of hyperkeratosis, and cracks (fissures) (Coenraads 2012). Lesions are associated with significant itching and pain. 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 health 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).

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. Type 2 helper T cell (Th2) mediated immune response is believed to play a central role in the pathogenesis of AD, including that of hand and foot. 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).

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

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

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 hand and foot explains the limited efficacy of topical anti-inflammatory agents.

There is no Food and Drug Administration (FDA) approved systemic therapy specifically 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.

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 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.

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.

Additional detailed background information can be found in the study protocol.

1.2. Study Objectives

1.2.1. Primary 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.

1.2.2. 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

1.2.3. 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

1.2.4. Modifications from the Statistical Section in the Final Protocol

The per protocol set (PPS) will be removed from the analysis since it is not applied in this study.

The secondary endpoints of change from baseline to week 16 in weekly average of daily hand and foot peak Pain NRS and change from baseline to week 16 in weekly average of daily Sleep NRS will be used instead of percent change from baseline to week 16 in weekly average of daily hand and foot peak Pain NRS and percent change from baseline to week 16 in weekly average of daily Sleep NRS since the majority of patients have small baseline values for weekly average of daily hand and foot peak Pain NRS and weekly average of daily Sleep NRS which will result in large percent change and standard deviation values.

1.2.5. Revision History for SAP Amendments

None.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 3, 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 are planned to be enrolled in this study.

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)

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 hand and foot 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.

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 on hands/feet. Patients will need to follow these measures throughout the screening period in order to remain eligible for the study. 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 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 EU). Randomization will be capped for 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. hand and foot 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 week 2 and week 4, and then in-clinic visits every 4 weeks through week 16 with bi-weekly phone visits in between the in-clinic visits. Safety laboratory tests, collection of samples for study drug concentrations, immunogenicity, and clinical assessments will be performed at specified clinic visits.

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.

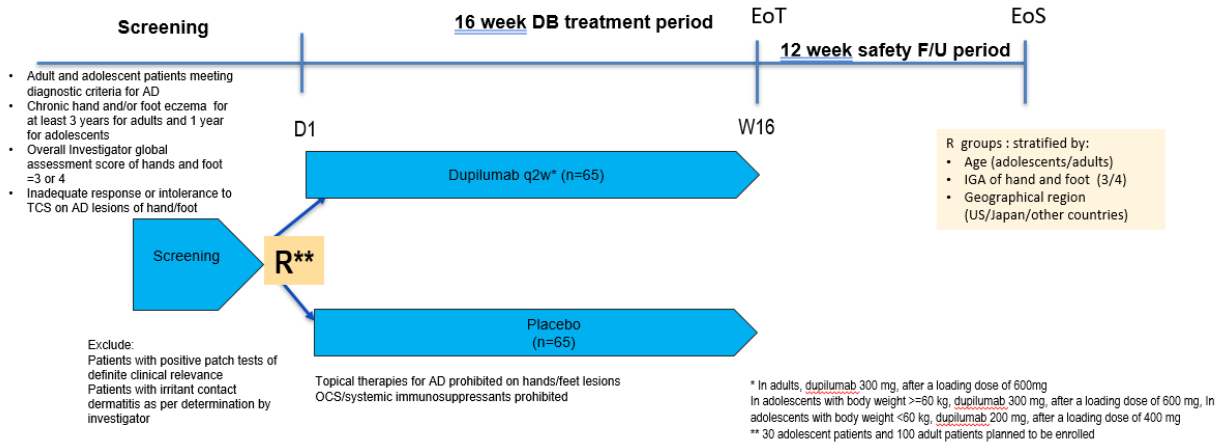
Patients may continue study treatment if they received rescue treatment.

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.

2.2. 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.

2.3. Sample Size and Power Considerations

It is reasonable to assume that the effect size of dupilumab on AD of hand and foot would be similar to that seen in global AD lesions in previously conducted phase 3 trials as the underlying pathophysiology is the 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).

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.

The sample size calculations were done using nQuery (7.0).

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis:

3.1. Efficacy Analysis Sets (FAS)

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

All efficacy variables will be evaluated on the FAS. Analysis on the FAS will be considered as primary.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive at least one dose of study drug and will be analyzed as treated. Treatment compliance/administration and all clinical safety variables will be summarized based on the SAF.

The actual treatment group as treated is defined to be the real received treatment:

- For a patient who received at least one dupilumab injections, the actual treatment will be assigned as dupliumab Q2W.
- For a patient who received all placebo injections, the actual treatment will be assigned as placebo.

For safety summaries, the following analysis periods are defined:

- week 16 treatment period is defined as
  - Time after the first dose of study drug to the date of week 16 visit if patients completed week 16 with known visit date.
  - Time after the first dose of study drug to study day 113 (16 weeks times 7 days/week), or to patient's last study participation date, whichever comes earlier, if patients did not complete week 16 visit or had missing week 16 visit date.
- Follow-up period is defined as the day after the end of treatment period to the patient last study participation date.

SAF will be the basis for the analyses for the treatment period; however, for the analyses for the follow-up period, only a subset of the corresponding SAF will be included, which is defined as the patients who entered the follow-up period and had at least one visit after week 16 visit.

3.3. The Pharmacokinetic Analysis Set (PKAS)

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

3.4. The Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all treated patients who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing ADA result following the first dose of study drug or placebo. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

The NAb analysis set (NAbAS) includes all treated patients (active or placebo) that are included in the ADA analysis set and that tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times and had at least one non-missing post-dose NAb result (either imputed or analysis result). Samples that tested negative for ADA are not assayed in the NAb assay and the corresponding NAb results are imputed as negative and included as such in the NAb analysis set. Patients in the NAbAS with multiple post-dose ADA results which consist of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), are set to NAb negative. Patients in the NAbAS that have at least one post-dose positive NAb analysis result are set to NAb positive even if other NAb results are missing.

3.5. Subgroups

Subgroups are defined by key baseline factors recorded on the eCRF and listed as follows. The analysis for the subgroups defined may not be performed if the number of patients within the subgroup is small, e.g. <10 patients per treatment arm. No subgroup analysis will be performed if the study fails to meet its primary objective, i.e. fails to test significant difference in primary and key secondary endpoints.

Subgroups are listed as follows:

Subgroups to be considered for primary efficacy analyses:

- Age group (12-<18 yrs., ≥18yrs.)
- Sex (Male, Female)
- Race (White, Black, Asian, Other)
- Age of onset of hand and foot dermatitis (<18 yrs., ≥18 yrs.)
- Baseline weight group (<60 kg, ≥60-<90 kg, ≥90 kg)
- BMI (overweight or obese as defined by BMI ≥ 25 in adults and ≥ 85th percentile for age and gender in adolescents, BMI<25 in adults and <85th percentile for age and gender in adolescents)
- Region for global submission (United States, Japan, EU)
- Baseline disease severity [moderate (hand and foot IGA=3) and severe (hand and foot IGA=4)]
- Baseline hand and foot peak Pruritus NRS (<7, ≥7)
- Hand and foot Surface area of involvement (<50%, ≥50%)

- AD outside hand and foot (no (IGA=0), mild (IGA=1,2), moderate to severe AD (IGA=3 or 4))
- Morphology of hand and foot AD (Chronic dry fissured, hyperkeratotic, dyshidrotic, others)
- Patients with positive patch test to one or more allergens (yes, no)
- Hand and foot involvement (hands only, hand and foot or feet only)
- Previous use of systemic immunosuppressants for hand and foot AD (Yes, No)
- Previous use of systemic cyclosporine for hand and foot AD (Yes, No)
- Previous usage of Alitretinoin (Yes, No)
- History of irritant contact dermatitis of hand and foot (yes/no)
- High risk occupation for hand eczema (yes/no)
- Smoking status (non smoker and past smoker, occasional current smoker (> 0 day/month and ≤ 25days/month), regular current smoker (> 25days/month))

Additional subgroups based on patient's baseline characteristics may be performed.

The following subgroups will be considered for safety analyses:

- Age group (12-<18 yrs., ≥18 yrs.)
- Sex (Male, Female)
- Race (White, Black, Asian, Other)
- Baseline weight group (<60 kg, ≥60-<90 kg, ≥90 kg)
- Region for global submission (United States, Japan, EU)

4. ANALYSIS ENDPOINTS

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Demographic variables: Age at screening (year), Age group (≥12 - <18, ≥18-<65, , ≥65), Sex (Male, Female), Ethnicity (Hispanic or Latino, Not-Hispanic or Latino), Race (White, Black or African American, Asian, Other), Region (United States, Japan, EU), Baseline weight (kg), Baseline weight with grouping (≥60kg, <60kg for adolescents, <60 kg, ≥60-<90 kg, ≥90 kg for adults), height (m), BMI, BMI with grouping (overweight, not overweight for adolescents, <25, ≥25-<30, ≥30 for adults), Smoking status (current smoker, past smoker, non smoker)
- Baseline characteristics: Duration of hand and foot AD), A**ge of onset of hand and foot AD (mean (sd), median q1, q3, min, max, <18 yrs, ≥18yrs.),** Morphology of hand and foot AD (chronic dry fissured, hyperkeratotic, dyshidrotic, others), Number of patients with hand and foot involvement (hands only, hand and foot, feet only), Number of patients with positive patch test (yes, no), Number of patients with history of irritant contact dermatitis (yes, no), Investigator's Global Assessment (IGA) of hand and foot score [IGA = 3, 4], Modified Total Lesion Sign Score (mTLSS) for hand and foot, hand and foot peak Pruritus Numerical Rating Scale (NRS), hand and foot skin peak pain Numerical Rating Scale (NRS), sleep Numerical Rating Scale (NRS), hand and foot Area Involvement of Atopic Dermatitis, Hand Eczema Severity Index (HECSI), Quality of Life in Hand Eczema Questionnaire (QoLHEQ), Duration of hand and foot AD, Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Work Productivity and Activity Impairment Questionnaire Plus Classroom Impairment Questions (WPAI+CIQ)

4.2. Medical History and Atopic Disease Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Information on conditions related to AD including diagnosis of hand and foot AD and AD treatment history, history of ACD, personal and/or family history of asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy, hives and other allergies due to medications, animals, plants, mold, dust mites, etc. are collected.

4.3. Prior / Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded using WHO Drug Dictionary (WHODD). Procedures will be coded using MedDRA.

Prior medications/procedures: medications taken, or procedures performed prior to administration of the first dose of study drug. Recent hand and foot AD topical treatments history within 6 months before the screening visit is collected. History of treatment with systemic

immunosuppressants for hand and foot AD (cyclosporine, systemic corticosteroids, methotrexate, azathioprine, alitretinoin and other treatments) will also be collected.

Concomitant medications/procedures (CMs/CPs): medications taken, or procedures performed following the first dose of study drug through the EOS visit.

- Concomitant medications/procedures during the 16-week treatment period are medications/procedures taken after the first dose up to the week 16 visit date or date of study day 113 if the week 16 visit date is missing. Medications/procedures taken during the 16-week treatment period and continued afterwards into the follow-up period will be counted only once as concomitant medications/procedures during the 16-week treatment period.
- Concomitant medications/procedures during the follow-up period are medications/procedures taken after the week 16 visit date to end of study.

Prohibited concomitant medications/procedures: Treatment with the following **concomitant medications** is prohibited during the study period:

- 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)	

The following **concomitant procedures** are prohibited during study period:

- 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

Blinded adjudication of prohibited concomitant medications and procedures will be performed by the medical monitor before database locks with documented procedures.

Rescue treatments (i.e. both medications and procedures):

Rescue treatment for worsening of AD of hand and foot 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 hand and foot 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 hand and foot. 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. Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication or procedure, indication, timing, frequency and the potential impact of the use of the medication or procedure. The rescue treatments will be adjudicated by the medical director (or medical monitor) with documented procedures.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variable

The primary endpoint in the study is:

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

Investigator Global Assessment (IGA) of Hand and Foot

The IGA for hand and foot 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 hand and foot on this scale. It is important that this assessment be limited to only the hand and foot and not be influenced by severity of AD lesions on other parts of the body. IGA score will be assessed at the scheduled and unscheduled clinic visits according to Appendix 11.2.

4.4.2. Secondary Efficacy Variables

The key secondary endpoints:

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

Hand and Foot Pruritus Numerical Rating Scale (NRS) 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.

Itch will be measured using a worst scratch/itch NRS that was developed and tested for the study-relevant age group. This is an 11-point scale (0 to 10) in which 0 indicates no scratching/itching while 10 indicates worst scratching/itching possible.

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. Clinical sites will check and remind patient to complete the diary at each visit. The baseline worst scratch/itch scale score is defined as the prorated average of the worst scratch/itch scale scores reported continuously for 7 days right before the baseline visit (i.e. study day -7 to day -1) with a minimun of 4 daily scores. For post-baseline worst itch scale score, the weekly mean of daily worst scratch/itch score is calculated as the average of the available reported daily worst scratch/itch score within the week with a minimun of 4 daily scores.

Other secondary efficacy endpoints (not necessarily in order of testing in statistical hierarchy):

- 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
- Change from baseline to week 16 in weekly average of daily hand and foot peak Pain NRS
- 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)

Hand and Foot Skin Pain Numerical Rating Scale (NRS)

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. Patients will be instructed on using the scale to record their hand and/or foot 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.

Sleep Numerical Rating Scale (NRS)

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. 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.

Modified Total Lesion Sign Score for Hand and foot

The Modified Total Lesional Sign Score is adapted for hand and foot; 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 hand and foot and not be influenced by severity of AD lesions on other parts of the body. The mTLSS for hand and foot will be assessed at time points according to the schedule of events table in Appendix 11.2.

Surface Area of Hand and Foot Involvement of Atopic Dermatitis

This assessment will be performed at time points according to Appendix 11.2. The hand and foot area assessment tool is provided in the study reference manual.

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 Appendix 11.2, The HECSI is provided in the study reference manual.

Quality of Life in Hand Eczema Questionnaire

The QoLHEQ will be assessed at time points according to Appendix 11.2.

The QoLHEQ is provided in the study reference manual.

Work Productivity and Activity Impairment Questionnaire (WPAI) Plus Classroom Impairment Questions (CIQ)

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 Appendix 11.2.

4.4.3. Exploratory Efficacy Variable(s)

- In patients with AD lesions on other parts of the body in addition to hand and foot;
  - Percent change in EASI score from baseline to week 16 (in patients who have EASI≥16 at baseline)
  - Percent change in HECSI score from baseline to week 16 (in patients who have EASI≥16 at baseline)
  - Proportion of patients with IGA score of 0/1 on hand and foot at week 16 (in patients with IGA=3 or 4 on hand and foot at baseline)
  - Proportion of patients with IGA score of 0/1 at week 16 (in patients with global IGA=3 or 4 at baseline)
  - Proportion of patients with EASI-75 at week 16 (in patients who have EASI≥16 at baseline)
  - Proportion of patients with HECSI-75 at week 16 (in patients who have EASI ≥ 16 at baseline)
  - Proportion of patients with EASI-50 at week 16 (in patients who have EASI ≥ 16 at baseline)
  - Proportion of patients with HECSI-50 at week 16 (in patients who have EASI ≥ 16 at baseline)
  - Proportion of patients with EASI-90 at week 16 (in patients who have EASI ≥ 16 at baseline)
  - Proportion of patients with HECSI-90 at week 16 (in patients who have EASI ≥ 16 at baseline)

Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (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 collected at the scheduled and unscheduled clinic visits according to Appendix 11.2. The EASI assessment tool is provided in the study reference manual.

4.5. Safety Variables

4.5.1. Adverse Events and Serious Adverse Events Variables

Adverse events (AE) and serious adverse events (SAE) will be collected starting from the time of informed consent signature and at each visit until the end of the study. All adverse events are to be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

The definition of AE and SAE are referred to protocol section 10.2.1 and section 10.2.2.

Pre-treatment AEs and treatment emergent AEs (TEAEs) are defined as follows:

- Pre-treatment AEs are AEs that developed or worsened in severity during the pre-treatment period, which is defined as the period from the patient providing informed consent up to the first dose of study drug.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered TEAEs.

AEs of Special Interest (AESI):

The following AESIs will be analyzed:

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

Other AEs:

Skin Infections on hand and foot (with adjudication by clinical), Herpes Infections on hand and foot and Injection Site Reactions will be analyzed.

Additionally other AEs such as Narrow and Broad Conjunctivitis CMQ will be analyzed.

- **Narrow conjunctivitis** CMQ is defined as the following PT terms
  - Conjunctivitis
  - Conjunctivitis allergic
  - Conjunctivitis bacterial
  - Conjunctivitis viral

  - Atopic Keratoconjunctivitis
- **Broad conjunctivitis** CMQ is defined as the following PT terms
  - Conjunctivitis
  - Conjunctivitis allergic
  - Conjunctivitis bacterial
  - Conjunctivitis viral
  - Atopic Keratoconjunctivitis
  - Blepharitis
  - Dry eye
  - Eye irritation
  - Eye pruritus
  - Lacrimation increased
  - Eye discharge
  - Foreign body sensation in eyes
  - Photophobia
  - Ocular hyperaemia
  - Conjunctival hyperaemia
  - Xerophthalmia

Note that, Appendix 11.4 provides a list of AESIs search criteria.

4.5.2. Laboratory Safety Variables

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 Appendix 11.2. 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 Appendix 11.2 .

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.

4.5.3. Vital Sign Variables

Vital signs (including pulse rate, sitting blood pressure, body temperature, and respiratory rate) will be collected pre-dose at time points according to Appendix 11.2. At the first administration of study drug, sitting blood pressure, respiratory rate and pulse rate will also be assessed at 30 minutes (+/- 10 minutes) post-injection.

4.5.4. Body Weight and Height

Body weight and height will be measured at time points according to Appendix 11.2.

4.5.5. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal. A thorough and complete physical examination will be performed at time points according to the schedule described in Appendix 11.2.

4.6. Pharmacokinetic (PK) Variables

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

4.7. Immunogenicity Variables

The immunogenicity variables include ADA status, NAb status and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.2. Samples positive in the dupilumab ADA assay will be further characterized for ADA titers and for the presence of NAb against dupilumab.

4.8. Biomarkers Variables

Not applicable.

5. STATISTICAL METHODS

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

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

All data will be summarized by 2 treatment groups:

- Dupilumab Q2W
- Placebo

5.1. Demographics and Baseline Characteristics

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

5.2. General Medical History and AD History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC, followed by PT, based on the overall incidence across treatment groups.

Information on conditions related to AD will be summarized and includes diagnosis of hand and foot AD and AD treatment history, history of ACD, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy hives and other allergies due to medications, animals, plants, mold, dust mites, etc..

All analyses will be based on the FAS population.

5.3. Prior/Concomitant Medications/Procedures

The number and proportion of patients taking prior/concomitant medications, prohibited medications and rescue medications will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined dupilumab treatment group. Patients will be counted only once for each medication class (ATC level 2 and 4) linked to the medication.

The number and proportion of patients taking prior/concomitant procedures, prohibited procedures and rescue procedures will be summarized, sorted by decreasing frequency of SOC and PT based on the overall incidence for the dupilumab treatment group. Patients will be counted only once for each SOC and PT linked to the procedure.

The number and proportion of patients taking adjudicated rescue treatment (concomitant topical treatments (medium to high potency TCS/TCI), systemic immunosuppressants) and/or other treatments (emollients/ antihistamines) will also be summarized separately.

The compliance with protocol requirements for application of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days

moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group.

Kaplan-Meier curves for time to first rescue use will be generated.

5.4. Subject Disposition

The following summaries will be provided for each treatment group and study total (unless otherwise specified):

- 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 (including COVID-19 related reasons)
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation (including COVID-19 related reasons)
- The total number of patients in each analysis set
- The total number of patients who entered the 12-week follow-up period
- Summary table of important protocol deviations (PDs) including PDs due to COVID-19 will be provided.

5.5. Extent of Study Treatment Exposure and Compliance

5.5.1. Measurement of Compliance

The compliance with protocol-defined study drug administration will be calculated as follows:

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

The summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

5.5.2. Exposure to Study Drug and Observation Period

The duration of treatment (Q2W dosing) exposure during the study in day is calculated as:

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

The calculations do not take into account temporary dosing interruption including due to COVID-19. The summary of exposure to study drug will include the number of study drug doses administered and the duration of exposure. Duration of exposure will be summarized for each treatment group using the number of patients, mean, SD, minimum, median, Q1, Q3, and maximum.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories cumulatively by these categories: ≥ 14 days, ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥ 70 days, ≥ 84 days, ≥ 98 days and ≥ 112 days with an increment of 2 weeks for each subsequent category.

The duration of observation period during the study in days is calculated as:

(Date of the last visit – date of the first study drug injection) +1.

The duration of observation period will be summarized descriptively using number of patients, mean, SD, median, Q1, Q3, minimum and maximum. In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest are specified as:

≥ 15 days, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥113 days, and ≥197 days.

5.6. Analyses of Efficacy Variables

The analyses of efficacy variables are described in the subsections below and summarized in Appendix 11.1.2. The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimands of interest for the primary endpoint and selected secondary endpoints are provided in Appendix 11.1.1.

5.6.1. Analysis of Primary Efficacy Variable

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 EU]).

Sensitivity analyses:

Sensitivity analysis using the last observation carried forward (LOCF) approach to determine patient's status at week 16 will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. The efficacy data will be set to missing after early termination due to AE and other reasons excluding rescue treatment , then the LOCF method will be used to determine patients' status at week 16.

To assess the robustness of primary analysis results, a delta-adjusting pattern-mixture approach for tipping point analysis (2013, Ratitch) under MNAR (missing not at random) assumption, will be conducted for the primary endpoint. The impact from missing data on the comparisons in proportion of patients achieving IGA 0/1 (co-primary endpoint: EASI-75, **only in European Union [EU] and EU Reference Market Countries**) at week 16 between dupilumab and placebo control group will be examined as follows.

- A sequence of analyses will be performed with the adjustment to artificially decrease the response rate in dupilumab group and increase the response rate in placebo group with a fixed and definite set of values for data imputation.

- For each combination of increasing response rate in placebo and decreasing response rate in dupilumab, multiple imputed datasets will be generated and analyzed using CMH test. The results obtained from multiple imputed datasets will be combined to generate statistical inference, i.e. p-value and treatment difference between 2 treatment groups.
- A "tipping point" will be identified while the result is no longer statistically significant (i.e. p-value >0.05).

5.6.2. Analysis of Secondary Efficacy Variable

All secondary endpoints will be evaluated based on the FAS population.

The binary secondary efficacy endpoints (e.g., improvement of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16) will be analyzed using the same approaches used for the analysis of the primary endpoints as described in Section 5.6.1.

The continuous endpoints (e.g., percent change mTLSS for hand/foot lesions from baseline to week 16) will be analyzed using analysis of covariance (ANCOVA) model 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 EU]), and relevant baseline value included in the model. 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. To be specific, the missing data will be imputed by postbaseline worst-observation-carried-forward (WOCF) if there is at least one non-missing postbaseline value or by baseline value if there is no postbaseline value. The multiple imputation (MI) approach will be used for the missing due to other reasons, including reasons due to COVID-19. The MI will be performed based on all observed data before the imputation by WOCF approach. To account for the uncertainty in the imputation, missing data from the FAS will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates including treatment groups, randomization strata (baseline weight group, baseline IGA and region), and relevant baseline.

Once imputations are made, the week 16 data of each of the 40 complete datasets will be analyzed using ANCOVA model with treatment, randomization strata (baseline weight group, baseline IGA and region), and relevant baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.

Onset of action analysis

Onset of action in percent change from baseline weekly average of daily hand and foot peak Pruritus NRS score can be assessed by providing a nominal p-value at each assessment visits. The

analysis will be carried out on the FAS population only. Using this analysis, the first assessment visit at which p <0.05 for the difference from placebo in the weekly average of daily worst scratch/itch NRS score that remains p < 0.05 at subsequent weekly measurements through week 16 can be identified. The similar analysis will be carried out on the following binary responses:-
Hand and foot IGA 0/1

- Improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS score ≥4 from baseline

Percent change in mTLSS for hand/foot lesions from baseline

To aid the interpretation of the percent change in mTLSS on hand and foot endpoint, measurement properties of the mTLSS on hand and foot were evaluated in blinded data on 65% of the target sample size (85 patients out of target sample size of 130). Using IGA on hand and foot as the anchor-measure, it was estimated that a median reduction of 50% to 75% in mTLSS score on hand and foot from BL to Week 16 can be considered clinically meaningful since it corresponds to a 1- to 2-point improvement in IGA on hand and foot. Therefore, a responder analysis will be conducted for dupilumab versus placebo at Week 2, 4, 8, 12, and 16 using the thresholds of at least 50% and at least 75% reduction in mTLSS on hand and foot from BL. Additionally, a empricical cumulative distribution function (CDF) curve will be generated by plotting the cumulative proportion of patients (Y axis) in dupilumab and placebo arm by the percent change in mTLSS on hand and foot from BL to Week 16 (x-axis) achieved.

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 CMH method adjusted by randomization strata based on LOCF imputation method will be performed as the sensitivity analyses of key secondary endpoint.

5.6.3. Adjustment for Multiple Comparison

Multiplicity Considerations

A hierarchical procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints of dupilumab versus placebo. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in below table (all comparisons are with the placebo).

Table 1: The Hierarchical Testing Order

Level	Efficacy Endpoints (EPs) at Week 16	Testing Order
Primary endpoint	Proportion of patients with IGA (hand and foot) 0 to 1 (on a 5-point scale)	1
Key Secondary endpoints	Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥4	2

Level	Efficacy Endpoints (EPs) at Week 16	Testing Order
Secondary endpoints	Percent change in mTLSS for hand/foot lesions from baseline	3
	Percent change from baseline in weekly average of daily hand and foot peak pruritus NRS	4
	Change from baseline in weekly average of daily hand and foot peak Pain NRS	5
	Percent change from baseline in Hand Eczema Severity Index (HECSI) score	6
	Proportion of patients with HECSI-75	7
	Change from baseline in percent surface area of hand and foot involvement with AD	8
	Change from baseline in QOLHEQ	9
	Change from baseline in weekly average of daily Sleep NRS	10

5.6.4. Subgroup Analysis

Subgroups for the primary endpoint and key secondary endpoint will be analyzed based on the FAS.

The analysis method for the subgroups will be the same as the primary analysis described in Section 5.6.1 as appropriate. If for any reason such as due to small number of patients in a subgroup, the model-based inferential statistics cannot be computed, or deemed inappropriate, only descriptive statistics will be provided.

Forest plots of the primary and key secondary efficacy endpoint across subgroups will be provided. Interactions between the subgroups and treatment groups will also be tested using the logistic regression model. The model will include randomization strata,treatment group, subgroup, and treatment by subgroup interaction as factors. P-values for the interaction term will be reported.

5.6.5. Analyses of Other Efficacy Variables

The analyses of other efficacy variables (binary and continuous endpoints) will be conducted in a similar fashion as the primary analysis described in Sections 5.6.1 and 5.6.2. unless otherwise noted in the individual descriptions of other efficacy variables or deemed inappropriate.

5.7. Analysis of Safety Data

The analysis of safety and tolerability will be performed based on the SAF.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination and vital signs.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables and vital signs are defined in Appendix 11.3. A treatment-emergent PCSV is any PCSV which developed or worsened in severity compared to baseline during the treatment and/or follow-up period. The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

In addition, the summary of safety results (including TEAEs, clinical laboratory, vital signs and ECG) will be performed for subjects who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic in each study part, respectively if deemed appropriate. The summary will be performed for pre-, during, and post-COVID-19 periods for patients impacted by COVID-19, if deemed appropriate.

5.7.1. Adverse Events

The number and proportion of patients reporting TEAEs will be summarized overall during the study, during the week 16 treatment period, and during the follow-up period separately, sorted by decreasing frequency of SOC and PT in the dupilumab group.

AE incidence tables will be presented by treatment group for the SAF as well as for selected subgroups. TEAE summaries will present the number (n) and percentage (%) of subjects experiencing a TEAE by SOC and PT, sorted by decreasing frequency of SOC and PT for the dupilumab treatment group. Multiple occurrences of AEs of the same PT (or SOC) in the same subject will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for subjects with multiple instances of the same event. The denominator for computation of percentage is the number of patients in each treatment group for the corresponding analysis period as specified in Section 3.2.

An overall summary of TEAEs will be provided with number and proportions of patients with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI)
- TEAE leading to death
- TEAE leading to permanent treatment discontinuation

Detailed summaries of TEAEs will include:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs (for HLTs: Injection site reactions, Herpes viral infections) by SOC/HLT/PT
  - TEAEs by PT
  - Common TEAEs by SOC/PT (incidence with PT ≥5%)
  - TEAEs by severity by SOC/PT

  - TEAEs related to study medication as assessed by the investigator by SOC/PT
- Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/PT
  - Serious TEAEs related to study medication as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- Fatal TEAE by SOC/PT
- AESI by AESI category (Appendix 11.4) and SOC/PT

5.7.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment emergent PCSVs. This summary will be provided based on the subgroup of SAF patients who did not meet the PCSV criterion at baseline.
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest.

5.7.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSV
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

5.8. Analysis of Pharmacokinetic Data

The following analyses will be conducted:

- Descriptive statistics of functional dupilumab concentrations in serum at each sampling time by dose
- Graphical presentations of median and mean (+/- SD) functional dupilumab concentration in serum vs nominal time profiles
- Graphical presentations of individual functional dupilumab concentration in serum vs actual sampling time profiles
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum.

No formal statistical analysis will be performed.

5.9. Analysis of Immunogenicity Data

5.9.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.7 will be summarized using descriptive statistics in the ADA analysis set.

Immunogenicity will be characterized by ADA status, ADA category and maximum titer observed in patients in the ADA analysis sets.

The ADA status of each patient may be classified as one of the following:

- Positive.
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 4-fold the baseline titer value.
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥4-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 12-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Transient - Not persistent or indeterminate, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples

The maximum titer category of each patient is classified as:

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
  - Number (n) and percent (%) of pre-existing patients
- Number (n) and percent (%) of treatment-emergent ADA-positive patients

  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA-positive patients

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.9.2. Analysis of Neutralizing Antibodies (NAb) Data

The absolute occurrence (n) and percent of patients (%) with NAb status in the NAb analysis set will be provided by treatment groups. The NAb status is categorized as follows:

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.
- Positive: Samples tested positive in the NAb assay.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Association of immunogenicity with exposure

Potential association between immunogenicity and systemic exposure to dupilumab will be explored by treatment groups. Plots of dupilumab concentration may be provided for analyzing the potential impact of ADA category, maximum titer category and NAb status on these profiles.

5.10.2. Immunogenicity and Safety/ Efficacy

The analyses in this section will only be performed if incidence of treatment emergent ADA positive response is sufficient to make meaningful conclusions (i.e. more than 5% in any treatment group).

Potential association between immunogenicity variables and safety events will focus on the following events:

- TEAEs
- Serious TEAEs
- TEAEs leading to permanent treatment discontinuation
- Injection site reaction
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylactic Reaction (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and the primary efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category in ADA positive patients
- NAb positive

5.11. Analysis of Biomarker Data

Not applicable.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Study Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment of the study for all measurements will be the latest available valid measurement taken prior to the first administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of worst scratch/itch scale is defined in Section 4.4.2.

The following rules specify the determination of baseline by both date/time information:

1. For the AE, lab, PK and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.

2. For other data except AE, lab, PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen- failure subject ID or enrolled subject ID.

6.2. General Data Handling Conventions

For the laboratory safety variables data, if the data fall below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention Missing Data

Missing data will not be imputed in the listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAE. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed, and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use the AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is ‘D’.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However, in order to simplify the programming flow, the imputation is proposed in line with the protocol which specifies to collect up to 2 years of prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date - 1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of follow up date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had a post-baseline PCSV but a missing baseline value will be regarded as having a treatment emergent PCSV.

6.4. Analysis Visit Window

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ADA) will be summarized by the study scheduled visits described in the study protocol and SAP "Schedule of Events". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination (ET) visit have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The analysis visit windows are created per study Schedule of Events (SOE) table for each parameter and will be applied if the data from study scheduled visits are unavailable. The following general rules will be applied to unscheduled visit and/or early termination (ET) visit mapping for each parameter.

1. If ET visit falls in an analysis window which already has no missing observed value of this parameter from the scheduled visit, ET will be mapped to the next scheduled visit.
2. If both ET visit and unscheduled visit of the same parameter are available in the same analysis visit window, only ET visit will be mapped.
3. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visits will be mapped using the following rules:

a. The closest unscheduled visit from the target day will be selected.
b. If multiple unscheduled visits exist on the same day, the first unscheduled visit will be used.

4. If mapping distance is greater than 2 weeks, the unscheduled visit will not be mapped.

Unscheduled visits and early termination (ET) visit will be mapped per the following analysis visit windows based on the visit schedule of each parameter as per Appendix 11.2

Table 2: Analysis Visit Window for Efficacy Endpoints: IGA(hand and foot), mTLSS, Hand and Foot Area Involvement, HECSI, and QOLHEQ

Visit from SOE	Target Day	Analysis Visit Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 2	15	[2, 22]
Week 4	29	[23, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 155]
Week 28	197	≥ 156

* Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date +1) when date of assessment ≥ 1st injection date; otherwise study day = (date of assessment – 1st injection date). If patient never received any dose of study drug, randomization date will be used in place of 1st injection date.

Table 3: Analysis Visit Window for Efficacy Endpoints: WPAI+CIQ, IGA(global) and EASI

Visit from SOE	Target Day	Analysis Visit Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 4	29	[2, 71]
Week 16	113	[72, 155]
Week 28	197	≥ 156

* Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date +1) when date of assessment ≥ 1st injection date; otherwise study day = (date of assessment – 1st injection date). If patient never received any dose of study drug, randomization date will be used in place of 1st injection date.

Table 4: Analysis Visit Window for Safety labs, Vitals, and PK

Visit from SOE	Target Study Day in Part B[a]	Vital signs, Weight	Physical examination, Height	Pregnancy Test	Lab*	PK, ADA
Screening	<1	<1	<1	<1	<1	<1
Baseline	1	1		1	1	1
Week 8	57			[2, 71]		
Week 12	85			[72, 99]		
Week 16	113	[2, 155]	[2, 155]	[100, 155]	[2, 155]	[2, 155]
Week 28	197	≥ 156	≥ 156	≥ 156	≥ 156	≥ 156

*Hematology, Blood Chemistry and Urinalysis.
Note that both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values for laboratory, vital signs or ECGs as well as the baseline values.

Rules for visit windows of ePRO data collected daily using eDiary:

For the daily collected ePRO data (e.g. Pruritus worst scratch/itch NRS, skin pain NRS, sleep quality NRS), the analysis visit windows will be implemented following the procedure below:

Step 1: Derive the study day,

If diary date ≥ 1st injection date, then diary study day=diary date – 1st injection date +1;

Otherwise diary study day=diary date – 1st injection date

Step 2: Windows are defined as diary study day -7 to -1 = BL, 1 to 7 = week 1, 8 to 14 = week 2, etc, with 7 days interval between visit windows.

7. INTERIM ANALYSIS

No interim analysis is planned.

8. TIMING OF STATISTICAL ANALYSIS

The primary analysis may be performed when the last patient completes 16 weeks of treatment duration in order to expedite the submission to regulatory agencies. No changes in the conduct of the study will be made based on this primary analysis. The assessment of co-primary and secondary endpoints performed during the analysis will be the final analysis of the co-primary endpoint and secondary endpoints. Hence, there will be no need for alpha adjustment due to the primary analysis.

In order to maintain study integrity (with respect to the post-treatment follow-up visits, safety visits, and analyses) in the event a decision is made to perform the primary analysis, 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.

9. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

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11. APPENDIX

11.1. Summary of Statistical Analyses

11.1.1. Summary of Primary Estimand for Primary Endpoint and Secondary Endpoints

Primary and Key Secondary Endpoints	Population	Intercurrent Event(s) and Handling 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) 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)	FAS	The intercurrent events will be handled in the following order: 1. Rescue treatment: if rescue treatment is received no matter treatment discontinuation occurs, patients will be considered as non-responders after such events (composite strategy). 2. Treatment discontinuation: data collected after treatment discontinuation without rescue treatment will be included in the analysis (treatment policy strategy). Note: if both treatment and rescue treatment occur, refer to rescue treatment handling strategy.	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.
Other Secondary endpoints			
Continuous Endpoints (e.g. Percent change in mTLSS for hand/foot lesions from baseline to week 16)	FAS	The intercurrent events will be handled in the following order: 1. Rescue treatment: data after rescue treatment will be assigned by the worst possible value (composite strategy). 2. Treatment discontinuation: data collected after treatment discontinuation without rescue treatment will be included in the analysis (treatment policy strategy). Note: if both treatment and rescue treatment occur, refer to rescue treatment handling strategy.	Missing data due to rescue treatment, AE, and lack of efficacy will be imputed by WOCF. Missing data due to other reasons will be imputed by MI.
Binary Endpoints (e.g. Proportion of patients with improvement (reduction) of weekly average of daily hand and foot peak Pruritus NRS ≥3 from baseline to week 16)	FAS	Will be analyzed with the same fashion as the primary endpoint of proportion of patients achieving an IGA score of 0 or 1 on hand and foot at week 16 .	

11.1.2. Summary of Efficacy Analyses

Parameter(s)	Analysis Populations	Endpoints	Primary Statistical Method	Supportive /Sensitivity Statistical Method	Subgroup Analysis
Investigator's Global Assessment (IGA) on hand and foot (Primary)	FAS, PPS	• IGA 0 to 1 (Categorical)	• CMH test adjusted by randomization strata (Age, IGA Severity and Region)	LOCF, Tipping point analysis, Use all observed data	Yes
hand and foot peak Pruritus NRS (NRS ≥4, key secondary)	FAS	Categorical: • NRS ≥3 • NRS ≥4 Continuous: • % change from baseline	•Categorical: CMH test adjusted by randomization strata for categorical variables • Continuous: Multiple imputation (MI) using pattern mixture ((MI-WOCF)) with ANCOVA for continuous variables	LOCF, Use all observed data for key secondary endpoint	Yes for NRS ≥4 No for other NRS endpoints
hand and foot Modified Total Lesion Sign Score (mTLSS)	FAS	• % change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
hand and foot peak Pain NRS	FAS	• % change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
Sleep NRS	FAS	• % change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables	No	No
hand and foot involvement with AD	FAS	• Change from baseline	Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA	No	No
hand dermatitis, HECSI	FAS	Continuous: • % change from baseline Categorical: • HECSI75 • HECSI50 • HECSI90	• Multiple imputation (MI) using pattern mixture (MI-WOCF) with ANCOVA for continuous variables • CMH test adjusted by randomization strata for categorical variables	No	No
IGA	FAS	• Proportion of patients with IGA score of 0/1 at week 16	CMH test adjusted randomization strata	No	No

Parameter(s)	Analysis Populations	Endpoints	Primary Statistical Method	Supportive /Sensitivity Statistical Method	Subgroup Analysis
EASI	FAS	• Percent change in EASI score from baseline to week 16 • Proportion of patients with EASI-75 at week 16	CMH test adjusted randomization strata	No	No

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	Yes for selected AE summary	No
Skin infection TEAE	SAF	Incidence of skin infection TEAE (excluding herpetic infections) through week 16	Descriptive summary (incidence)	No	No
TE-SAE	SAF	Incidence of treatment-emergent serious adverse events (SAE) through week 16	Descriptive summary (incidence)	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No

11.2. 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											

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		
Assign anatomical area of involvement[10]			X											
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

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		
Patient assessment of hand and foot skin pain and sleep NRS[16]	X	X	X	X	X						X	X		
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

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		
Urinalysis	X		X								X	X	X	X
Pregnancy test, WOCBP only	Serum		Urine				Urine		Urine		Urine	Urine	Urine	Urine
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.

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 hand and foot.

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.
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
    - Hand and foot
    - 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 hand and foot. 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 hand and foot.
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.

11.3. Criteria for Treatment-Emergent Potentially Clinical Significant Value

Parameter	Adolescents (≥12 to <18)	Comments for Adolescents (≥12 to <18)	Adults (≥18)	Comments for Adults (≥18)
Clinical Chemistry				
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	≥1.3 ULN and baseline < 1.3 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Based on normal range: <1 mg/dL, CF = mg x 1.7 = µmol Concept paper on DILI – FDA draft Guidance Oct 2007.	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin ≥1.3 ULN)	Conjugated bilirubin will be measured when the total bilirubin is above the ULN Based on normal range: 0 to 0.4 mg/dL	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	(ALT≥3 ULN and TBILI≥2 ULN) and baseline (ALT <3 ULN or TBILI <2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
CPK*	≥3 ULN and baseline < 3ULN	FDA Feb 2005. Am J Cardiol April 2006.	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥132µmol/L and baseline < 132µmol/L (or ≥1.5 mg/dL and baseline <1.5 mg/dL) >=30% change from baseline	Benichou C., 1994 Two independent criteria	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	>8.0 mg/dL and ≤8.0 mg/dl at baseline (or >476 µmol/L and ≤476 µmol/L at baseline ≤2 mg/dL and >2 mg/dL at baseline (or ≤119 µmol/L and baseline > 119 µmol/L)		>408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥20 mg/dL and <20 mg/dL at baseline (or >=7.14 mmol/L and <7.14 mmol/L at baseline)		≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
Chloride Hypochloremia Hyperchloremia	<80 mmol/L and baseline ≥ 80 mmol/L ≥115 mmol/L and baseline < 115 mmol/L	Two independent criteria Reference ranges are same in adolescents (12-17 yrs. old) and adults	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	<129 mmol/L and baseline ≥ 129 mmol/L ≥150 mmol/L and baseline <150 mmol/L	Two independent criteria Reference ranges are similar in adolescents (12-17 yrs. old) and adults	≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	≤3.5 mmol/L and baseline >3.5 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria Reference ranges are similar in adolescents (12-17 yrs. old) and adults	<3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Calcium total	<2 mmol/L and baseline ≥2 mmol/L (or ≤ 8 mg/dL and baseline >8 mg/dL) ≥2.9 mmol/L and baseline <2.9 mmol/L (or ≥11.6 mg/dL and baseline <11.6 mg/dL)			
LDL Cholesterol	≥4.91 mmol/Land <4.91 mmol/L at baseline (≥ 190 mg/dl and <190 mg/dl at baseline)	Threshold for therapeutic intervention with pharmacotherapy in children (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011).		

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
Total Cholesterol	≥6.20 mmol/Land < 6.20 mmol/L at baseline (or ≥ 240 mg/dL and < 240 mg/dL at baseline)		≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	Fasting level ≥ 5.64 mmol/Land < 5.64 mmol/L at baseline (or ≥ 500 mg/dL and < 500 mg/dL at baseline)	Threshold for therapeutic intervention with pharmacotherapy in children. (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011). CF = g x 1.14 = mmol	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose Hypoglycaemia Hyperglycaemia	<2.7 mmol/L and ≥2.7 mmol/L at baseline (or < 50 mg/dL and ≥ 50 mg/dL at baseline) ≥10 mmol/L (unfasted) and < 10 mmol/L (unfasted) at baseline (or ≥180 mg/dl and <180 mg/dl at baseline); ≥7 mmol/L (fasted) and <7 mmol/L (fasted) at baseline (or ≥120 mg/dL and <120 mg/dL at baseline)		(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA May 2005. ADA Jan 2008.
HbA1c	>6.5% and <= 6.5% at baseline	WHO 2006/2011 ADA 2003 and 2012	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	Reference ranges are same in children (6-17 yrs. old) and adults	≤25 g/L and >25 g/L at baseline	
CRP			>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology				

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
WBC	<4.0 Giga/L and ≥4.0 Giga/L at baseline >13.5 Giga/L and ≤13.5 Giga/L at baseline		<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	<0.6 Giga/L and ≥0.6 Giga/L at baseline >6.0 Giga/L and ≤6.0 Giga/L at baseline		>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>1.2 Giga/L and <= 1.2 Giga/L at baseline		>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils			>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
Hemoglobin	<10 g/dL and >10 g/dL at baseline (or <100 g/L and >=100 g/L at baseline) ≥20 g/dL and <20 g/dL at baseline (or >=200 g/L and <200 g/L at baseline)	Two criteria are independent	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	For males: <0.37 v/v and ≥0.37 v/v at baseline; >0.52 v/v and ≤0.52 v/v at baseline For females: <0.33 v/v and ≥0.33 v/v at baseline <0.47 v/v and ≥0.47 v/v at baseline	Two Criteria are independent	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent
RBC			Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
Platelets	<100 Giga/L and ≥100 Giga/L at baseline >700 Giga/L and ≤ 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis				
Ketonuria	Presence and absence at baseline	Semi-quantitative methods		
Glycosuria	Presence and absense at baseline	Semi-quantitative methods		
Microscopic Hematuria	> 5 RBCs/ HPF and ≤5 RBCs/ HPF at baseline	Semi-quantitative methods		
Proteinuria	≥ 1+ and <1 at baseline	Semi-quantitative methods, ≥ 1+ means concentration >=30 mg/dL		
pH			≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs				
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm		≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	Hypotension: SBP<5th percentile for gender, age and height; baseline >=5th percentile **and** decrease from baseline ≥20 mmHg Hypertension: At or above the 95th percentile for age, sex and height postbaseline; baseline < 95% percentile; **and** increase from baseline ≥20 mmHg	Based on definition of hypotension as SBP<5th percentile for gender, age and height Based on definition of Hypertension as average SBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
DBP	Hypotension: DBP<5th percentile for gender, age and height; baseline >=5th percentile and decrease from baseline ≥10 mmHg Hypertension: At or above the 95th percentile for age, sex and height postbaseline; baseline < 95% percentile and increase from baseline ≥10 mmHg	Based on definition of Hypertension as average DBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Temperature	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary: >99 °F/37.2 °C			
Respiratory rate	<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline			
Weight	≥5% decrease from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007.	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG				
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm		≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥200 ms and < 200 ms at baseline		≥220 ms and increase from baseline ≥20 ms	
QRS	≥110 ms & < 110 ms at baseline		≥120 ms & < 120 ms at baseline	

Parameter	**Adolescents (≥12 to <18)**	**Comments for Adolescents (≥12 to <18)**	**Adults** (≥18)	**Comments for Adults** (≥18)
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female Additional: ≥500 ms and < 500 ms at baseline Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	Bazett's formula (measured QT interval divided by the square root of the R-R) to be applied to arrive at corrected QT value interval) QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. independent criteria	Absolute values (ms) Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. 5 independent criteria

11.4. Search Criteria for TEAE of Special Interest

Below table is the search criteria for AESI under protocol amendment 2.

AESI	**Search Criteria**
Anaphylactic reactions	Narrow SMQ for anaphylactic reaction
Systemic hypersensitivity reactions	Narrow SMQ for "hypersensitivity" ***minus*** SMQ (Narrow) Anaphylactic reaction Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Helminthic infections	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection
Any severe type of conjunctivitis or blepharitis	Broad CMQ conjunctivitis (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Ocular hyperaemia, Conjunctival hyperaemia, Xerophthalmia); AND Blepharitis PTs (Blepharitis, blepharitis allergic); AND Serious AE= "Yes" OR Severity= "severe"
Keratitis	Narrow SMQ for "corneal disorders"

Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	HLT = Eosinophilic disorders PT = Eosinophil count increased Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.

11.5. Algorithm for RESCUE TREATMENTS

1. Not required to adjudicate rescue treatment:

Post-baseline medications (WHODD-coded) given for indications consistent with AD of hands and feet.

a. Always considered rescue:
- ATC2 = CORTICOSTEROIDS FOR SYSTEMIC USE
- ATC2 = IMMUNOSUPPRESSANTS
- Preferred Drug Name = Ciclosporin
- Preferred Drug Name = Methotrexate
- Preferred Drug Name = Mycophenolate sodium
- Preferred Drug Name = Mycophenolic acid
- Preferred Drug Name = Mycophenolate mofetil
- Preferred Drug Name = Azathioprine
- Preferred Drug Name = Alitretinoin

b. Never considered rescue:
- ATC2 = EMOLLIENTS AND PROTECTIVES
- ATC2 = VASOPROTECTIVES
- ATC2 = ANALGESICS
- ATC2 = ANTI-ACNE PREPARATIONS
- ATC2 = TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
- ATC2 = ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
- ATC2 = ANTIVIRALS FOR SYSTEMIC USE
- ATC2 = ANTIFUNGALS FOR DERMATOLOGICAL USE
- ATC2 = ANTISEPTICS AND DISINFECTANTS
- ATC2 = ANTIHISTAMINES FOR SYSTEMIC USE
- ATC2 = ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.
- ATC2 = GENERAL NUTRIENTS
- ATC2 = VITAMINS
- ATC2 = DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
- ATC2 = OPHTHALMOLOGICALS

- ATC2 = ANTIINFLAMMATORY AND ANTIRHERUMATIC PRODUCTS
- ATC2 = PSYCHOLEPTICS
- ATC1 = ANTIINFECTIVES FOR SYSTEMIC USE
- ATC1 = BLOOD AND BLOOD FORMING ORGANS
- ATC1 = ALIMENTARY TRACT AND METABOLISM
- ATC1 = MUSCULO-SKELETAL SYSTEM
- ATC2 = COUGH AND COLD PREPARATIONS
- ATC2 = CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, if used before day 15
- Preferred Drug Name = Tacrolimus, if used before day 15
- Preferred Drug Name = Pimecrolimus, if used before day 15
- Preferred Drug Name = Crisaborole, if used before day 15

A blinded review of all post-baseline medications to adjudicate rescue treatment, based on medical judgement, may be performed in addition. A listing of treatments classified as rescue/non-rescue in a manner inconsistent with the classification under #1 will be provided, along with supporting rationale.

2. Required to adjudicate rescue treatment:

· All other medications (not noted in **1** above) given for indications consistent with hand and foot AD

Medications noted in **1a** above, when given for indications not consistent with hand and foot AD. Medications in 1a above when given for generalized AD will be considered rescue.

Below is a list of indications consistent with AD based on PT level from concomitant medication/procedure data using MedDRA dictionary

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
Infections and infestations	Bacterial infections NEC	Eczema impetiginous	10051890
Infections and infestations	Skin structures and soft tissue infections	Dermatitis infected	10012470
Infections and infestations	Skin structures and soft tissue infections	Eczema infected	10014199
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis	10012431
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis atopic	10012438
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Eczema	10014184
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Neurodermatitis	10029263

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